



Van afweer tot therapie: hoe we ons immuunsysteem kunnen benutten om ziektes te bestrijden



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KNOWLEDGE IN ACTION

**FACULTEIT GENEESKUNDE EN
LEVENSWETENSCHAPPEN**

Bieke Broux, PhD
27 november 2019

Overzicht



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**FACULTEIT GENEESKUNDE EN
LEVENSWETENSCHAPPEN**

- Wie ben ik?
- Het immuunsysteem
 - Aangeboren
 - Verworven
 - T cel respons en effectormechanismen
- Tumورimmunologie
 - T-cel respons en ontwikkelingsmechanismen
 - Nieuwe immuuntherapieën:
 - Immune checkpoint inhibitoren
 - DC-vaccinatie
 - CAR-T
- Auto-immuniteit
 - “Schoolvoorbeeld” multiple sclerose
 - Nieuwe immuuntherapieën:
 - Antilichaamtherapie
 - Celtherapie



Wie ben ik?



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- 2003-2007: bachelor/master Biomedische Wetenschappen (LUC-UH)



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- 2007-2013: doctoraat Biomedische Wetenschappen (als assistent)
- 2013-2015: postdoc Montréal (Canada)



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- 2007-2013: doctoraat Biomedische Wetenschappen (als assistent)
- 2013-2015: postdoc Montréal (Canada)
- 2016-nu: postdoc BIOMED-UH en mama



Het immuunsysteem

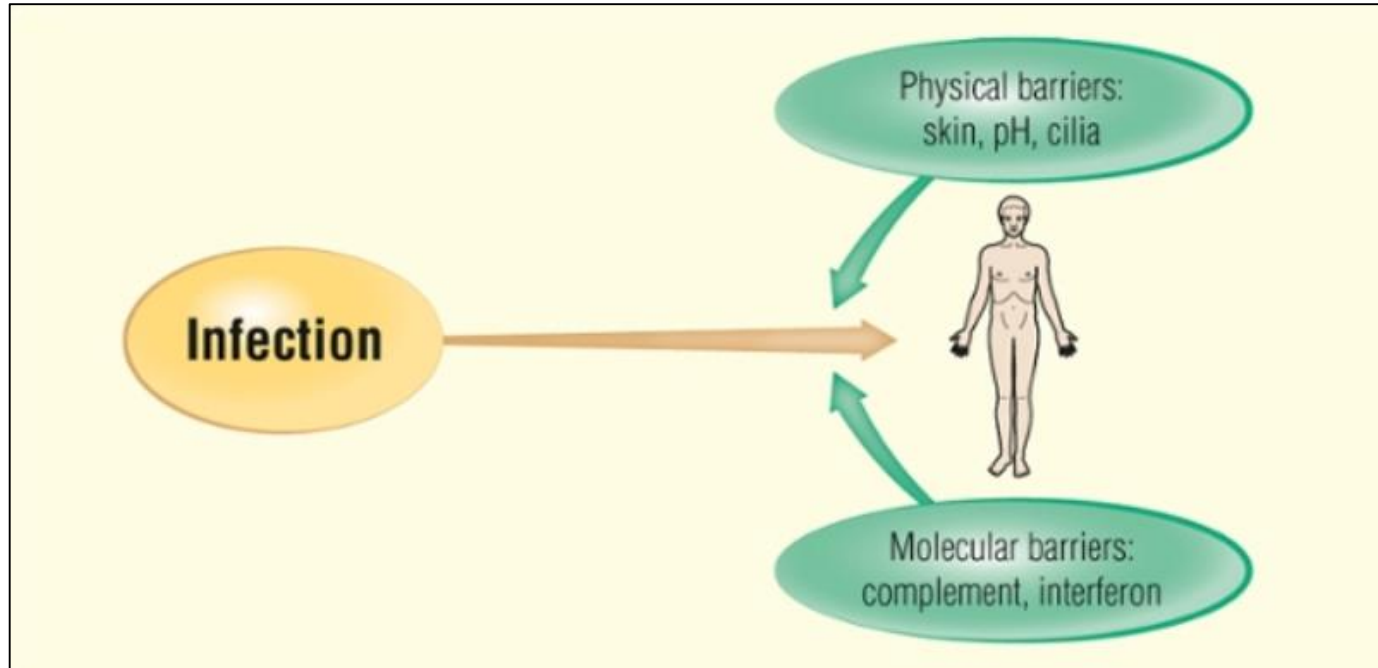


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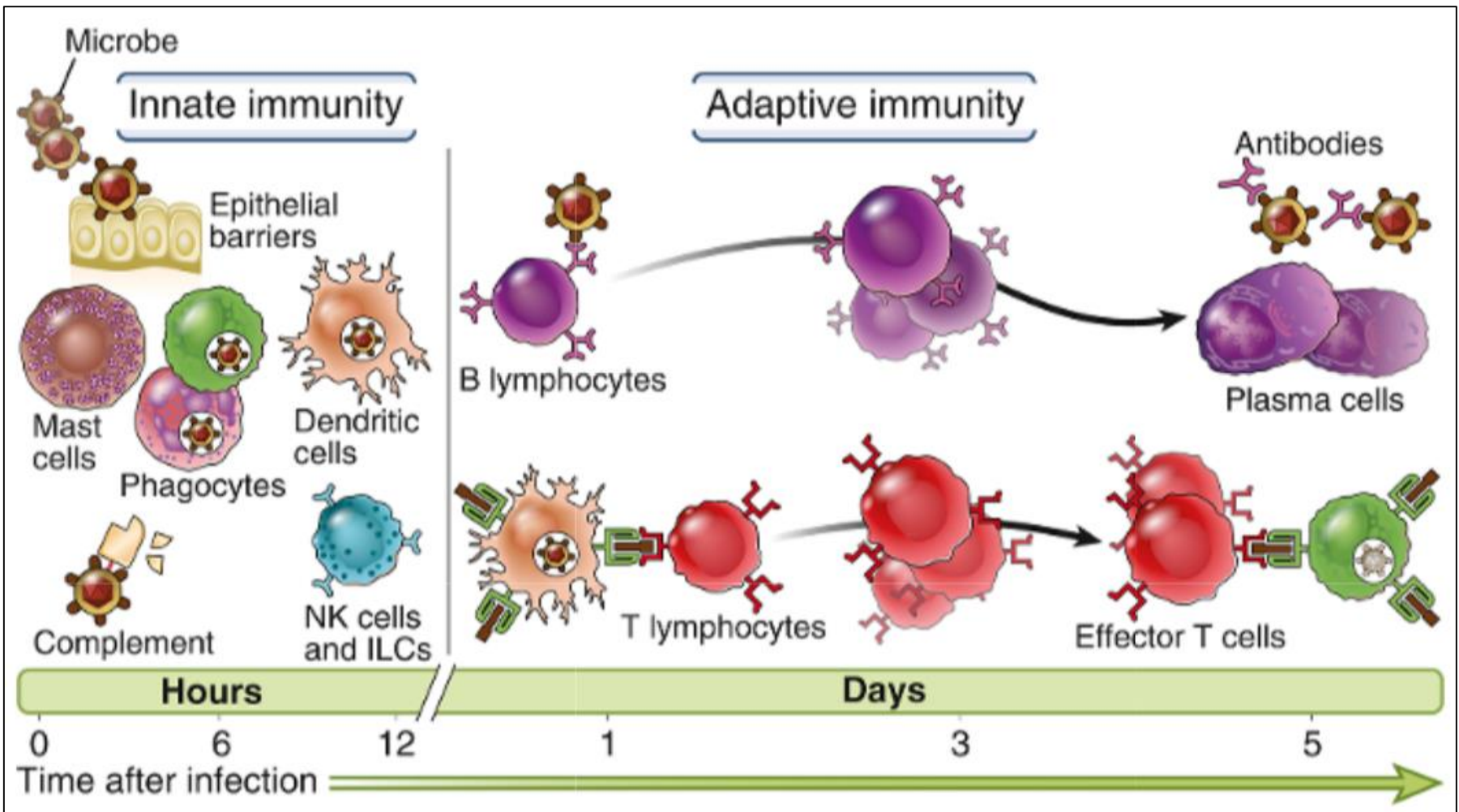
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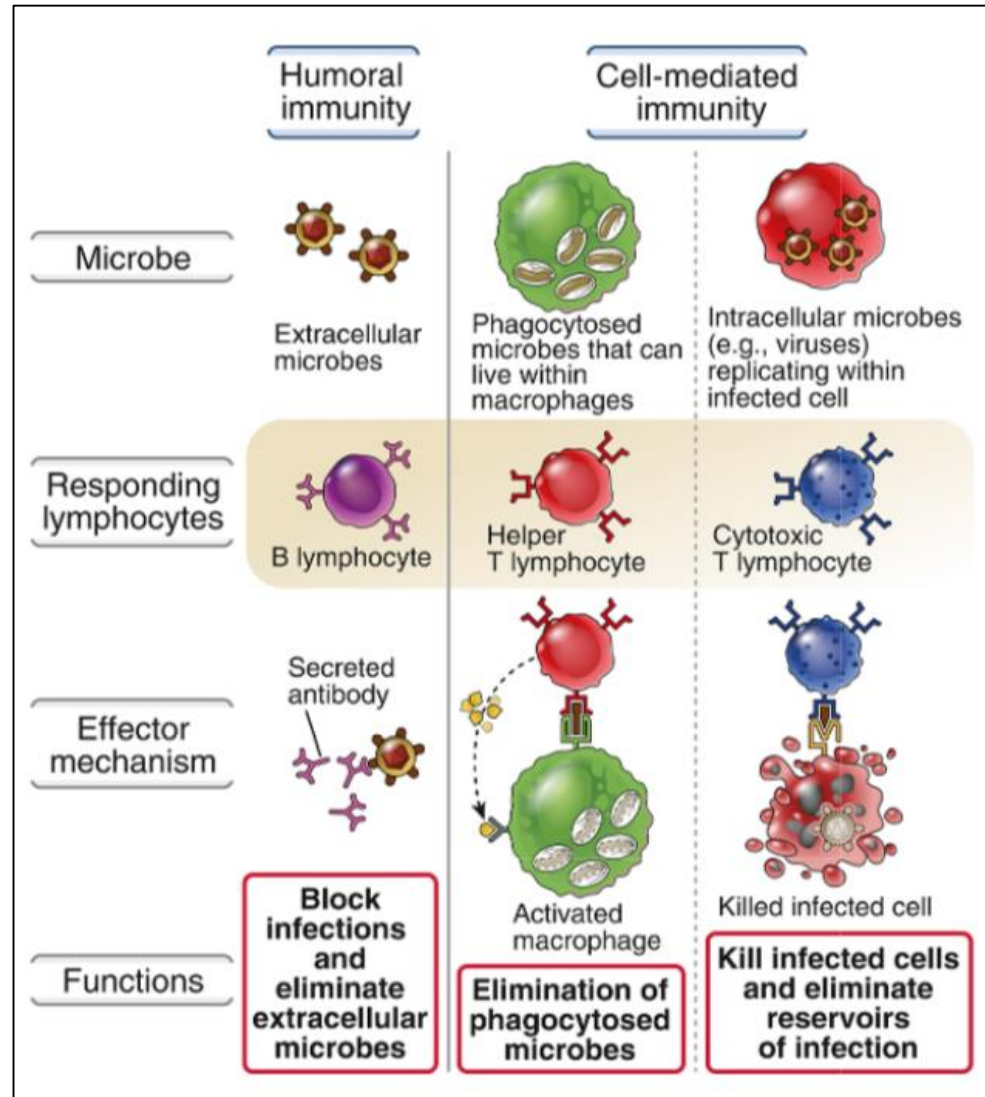
Het immuunsysteem



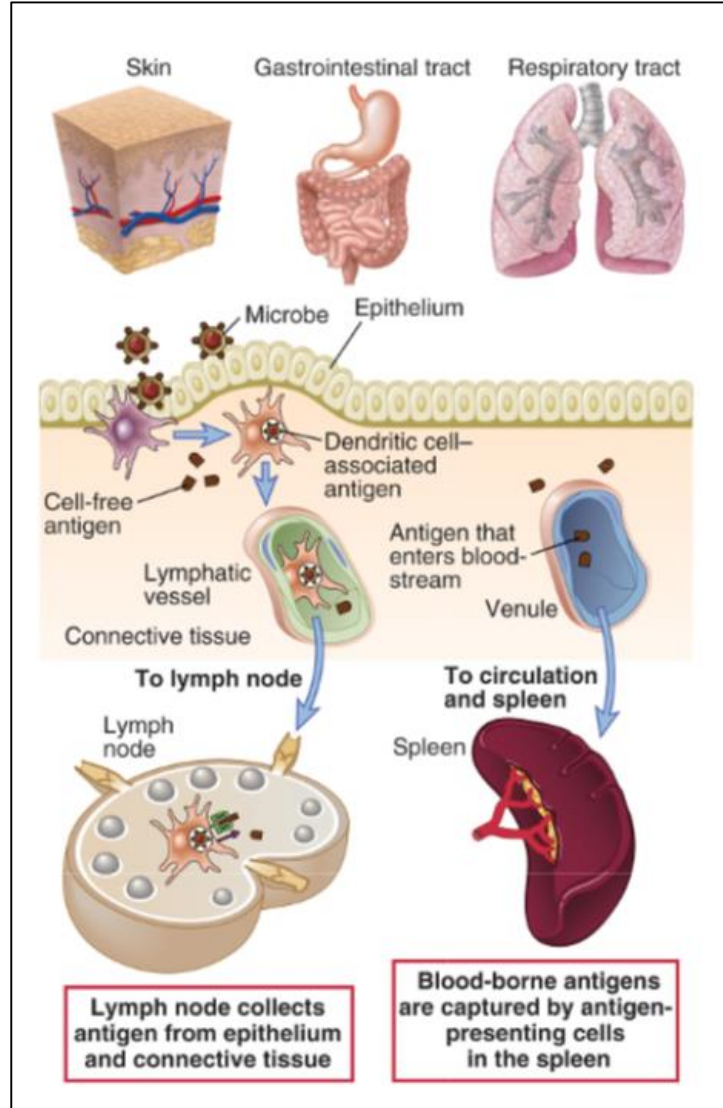
Aangeboren vs verworven



Types verworven immunresponsen



Vangen en presenteren van microbiële antigenen



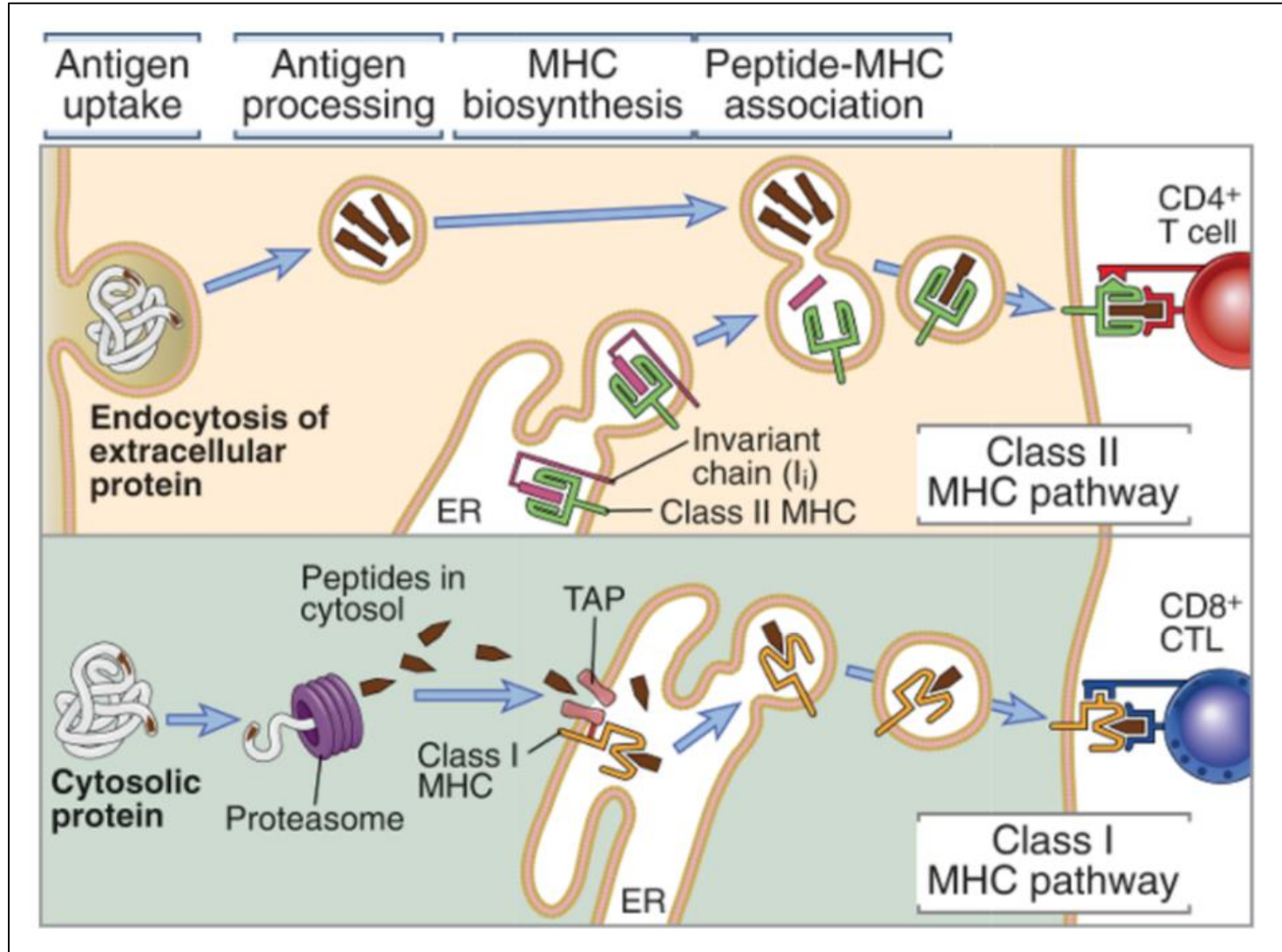
Fysieke barrière

Weefsel APC

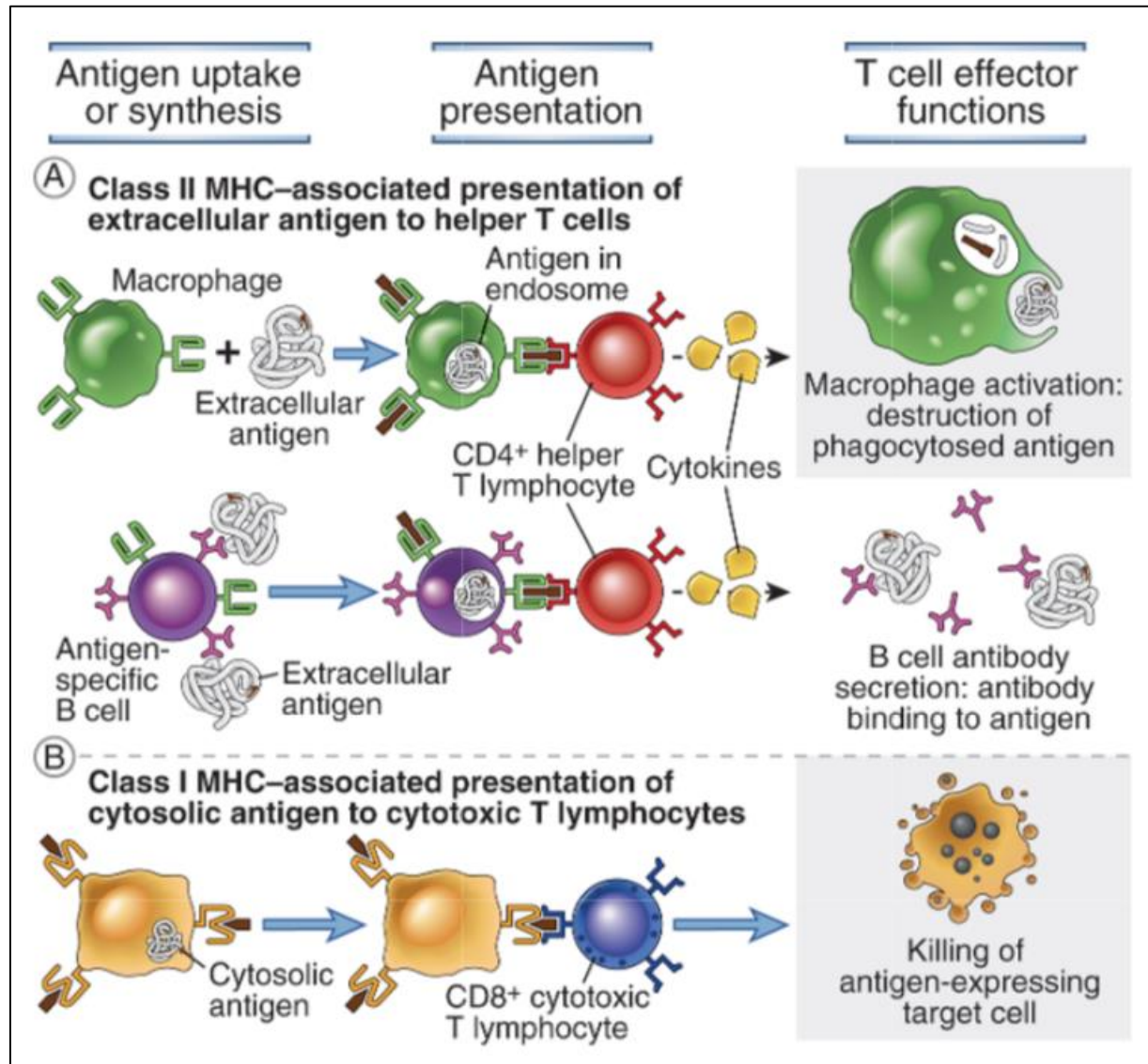
Secundaire lymfoïde organen



Antigen presentatie aan T-cellen



Effector functions van T-cellen

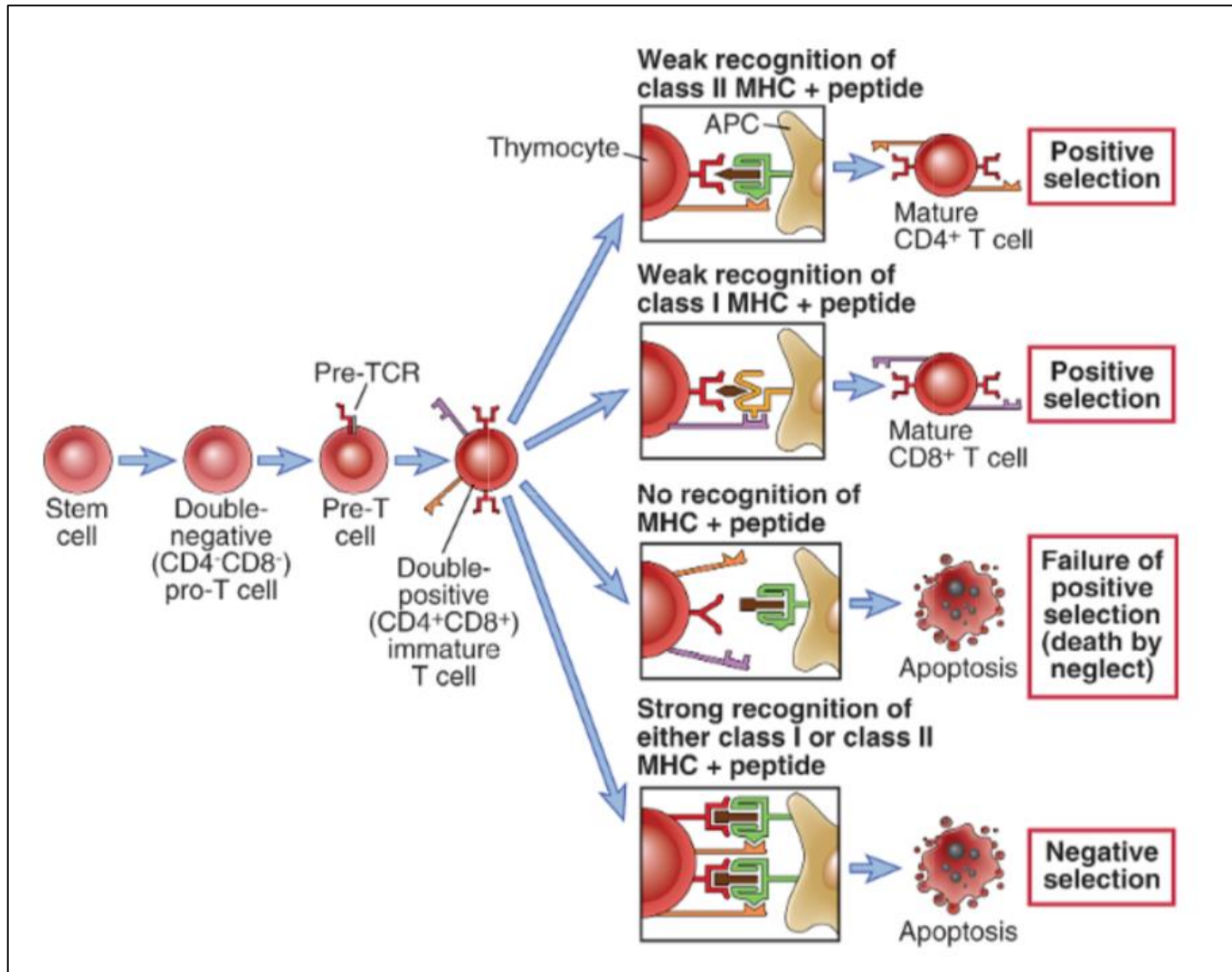


Antilichaam vs T cel receptor

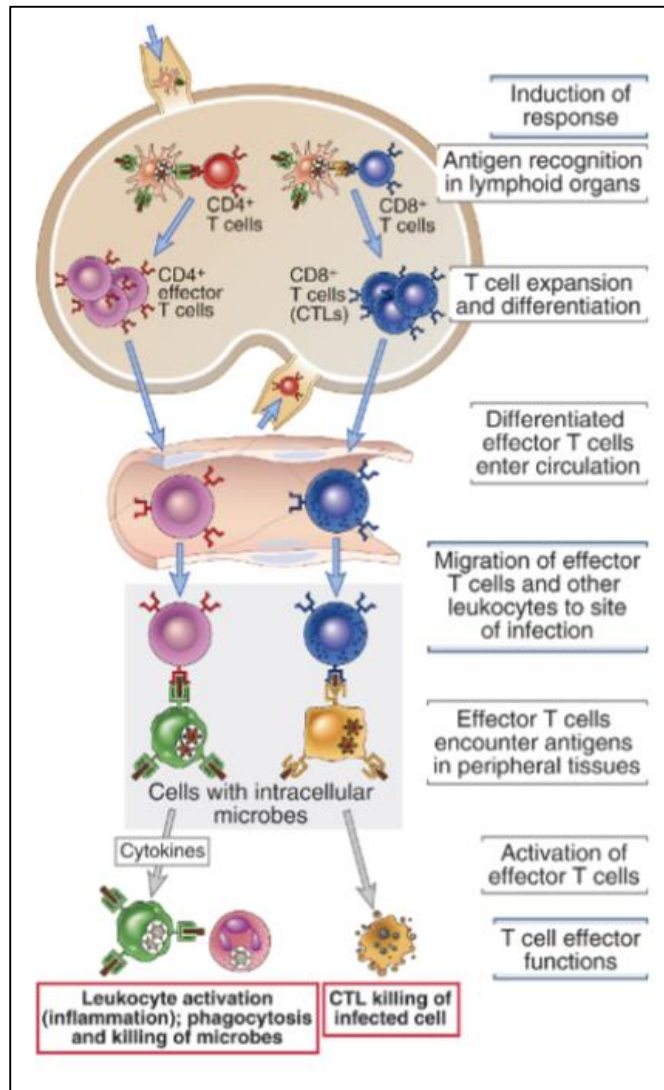
Feature or function	Antibody (Immunoglobulin)	T cell receptor (TCR)
	<p>Membrane Ig</p> <p>Antigen</p> <p>Igα</p> <p>Igβ</p> <p>Signal transduction</p> <p>Secreted antibody</p> <p>Effector functions: complement fixation, phagocyte binding</p>	<p>Antigen-presenting cell</p> <p>MHC</p> <p>Antigen</p> <p>TCR</p> <p>CD3</p> <p>ζ</p> <p>Signal transduction</p>
Forms of antigens recognized	Macromolecules (proteins, polysaccharides, lipids, nucleic acids), small chemicals Conformational and linear epitopes	Peptides displayed by MHC molecules on APCs Linear epitopes
Diversity	Each clone has a unique specificity; potential for $>10^9$ distinct specificities	Each clone has a unique specificity; potential for $>10^{11}$ distinct specificities
Antigen recognition is mediated by:	Variable (V) regions of heavy and light chains of membrane Ig	Variable (V) regions of α and β chains
Signaling functions are mediated by:	Proteins (Ig α and Ig β) associated with membrane Ig	Proteins (CD3 and ζ) associated with TCR
Effector functions are mediated by:	Constant (C) regions of secreted Ig	TCR does not perform effector functions



Selectie van T-cellen



Cellulaire immuunrespons



Secundaire lymfoïde organen

Migratie naar plaats van inflammatie

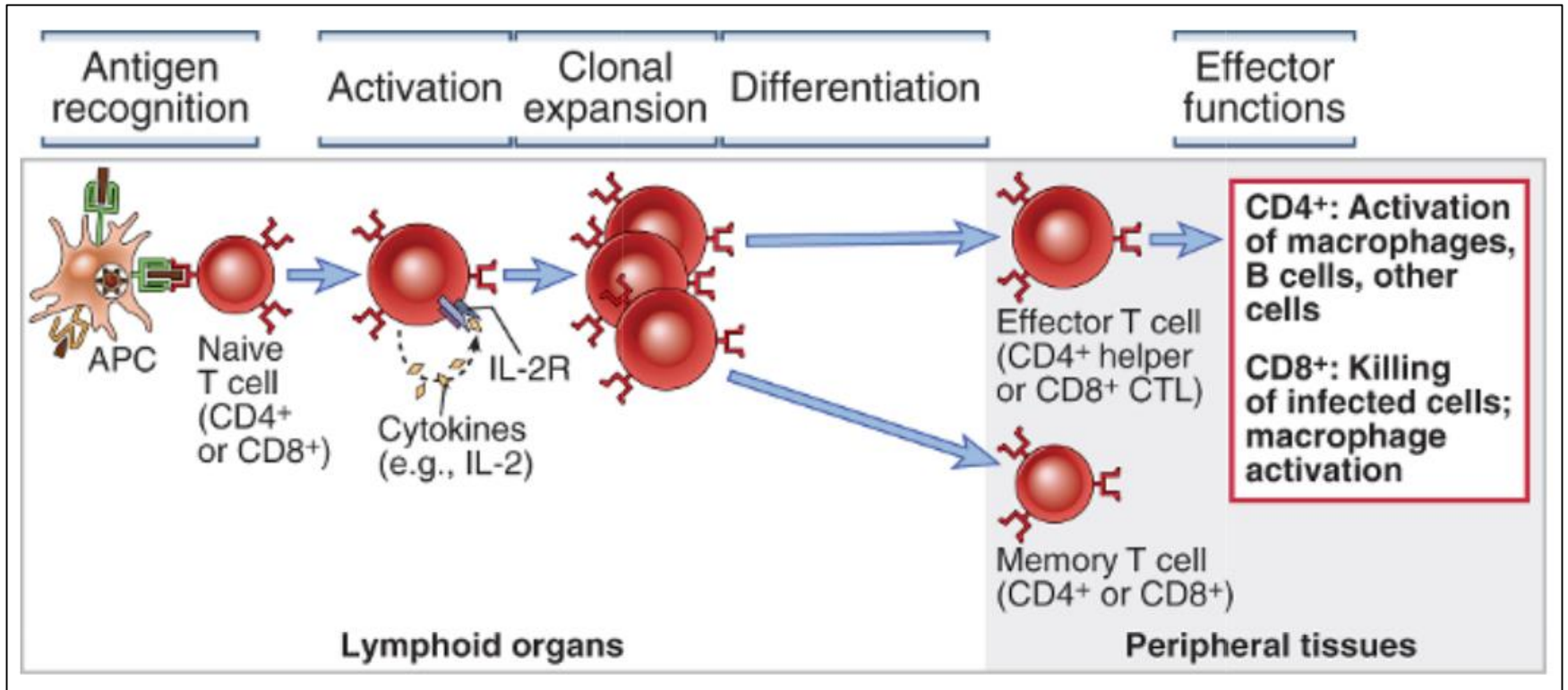
Lokale reactivatie

Effectorfunctie:

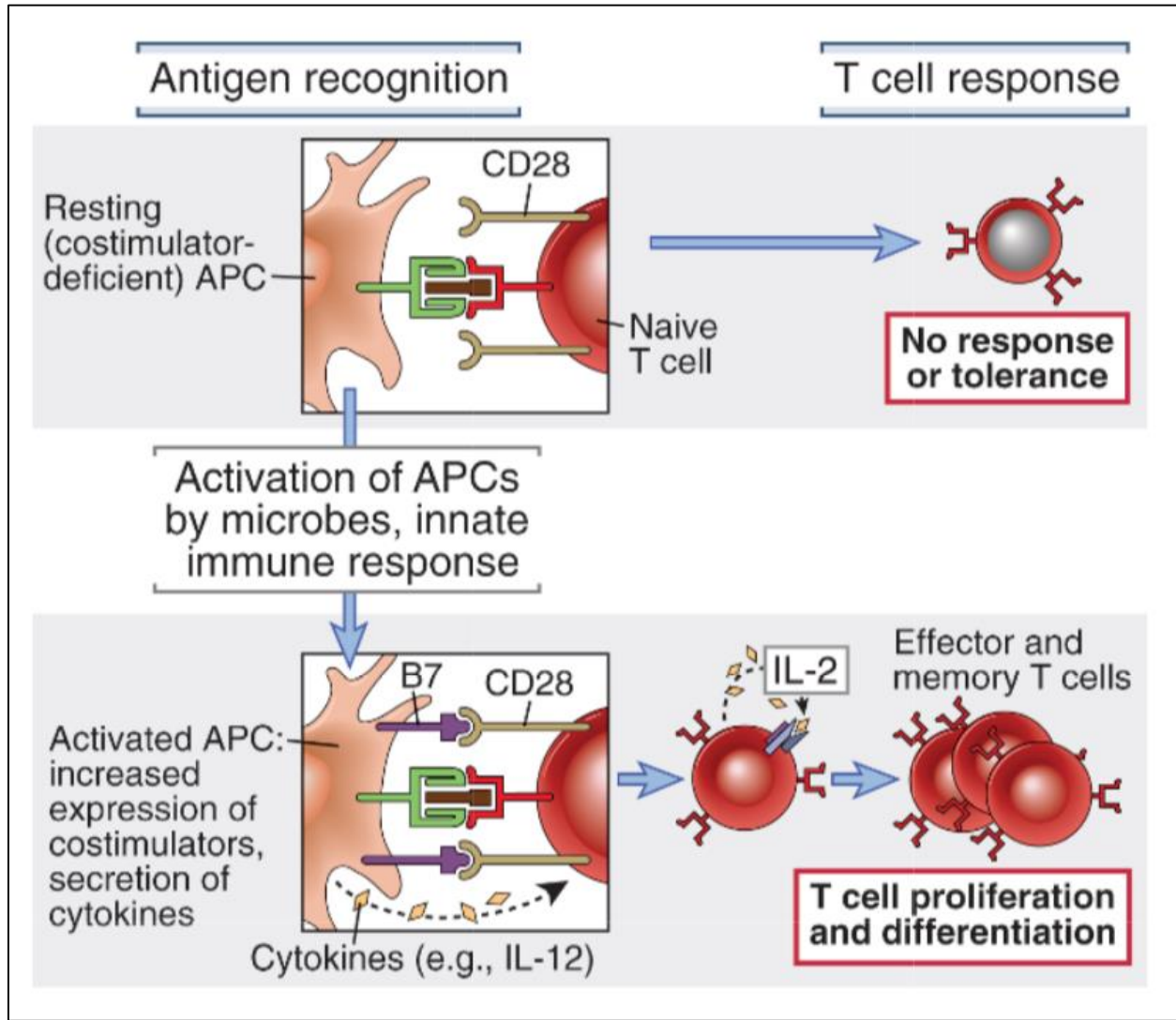
- Cytokineproductie
- Cytotoxiciteit



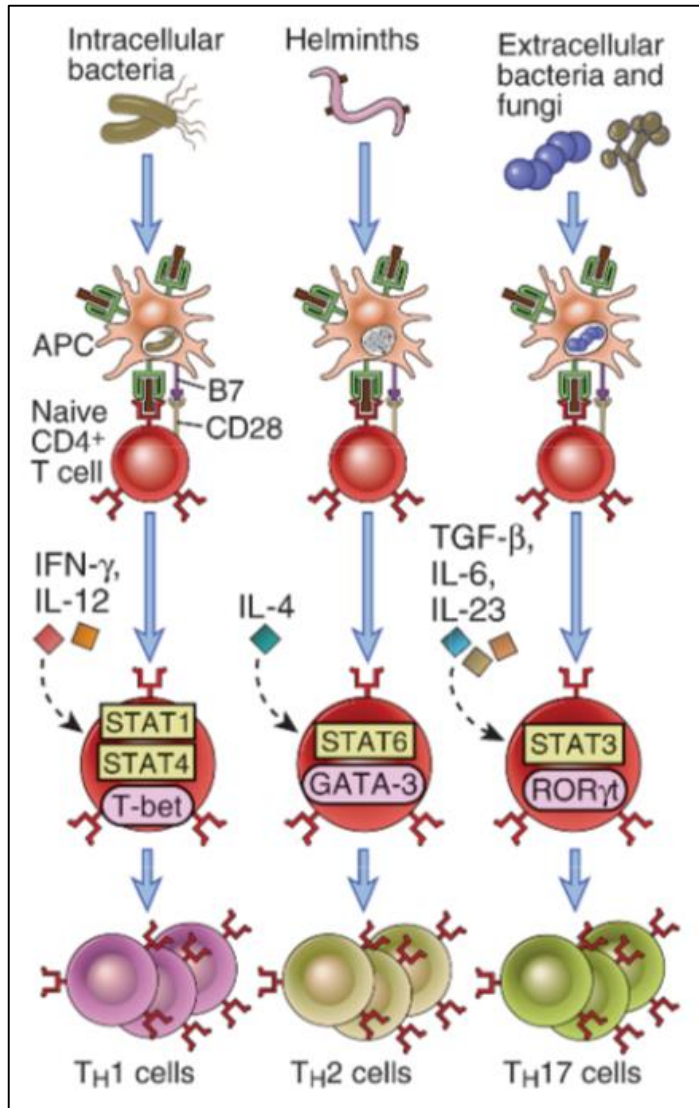
T cel activatie



T cel activatie



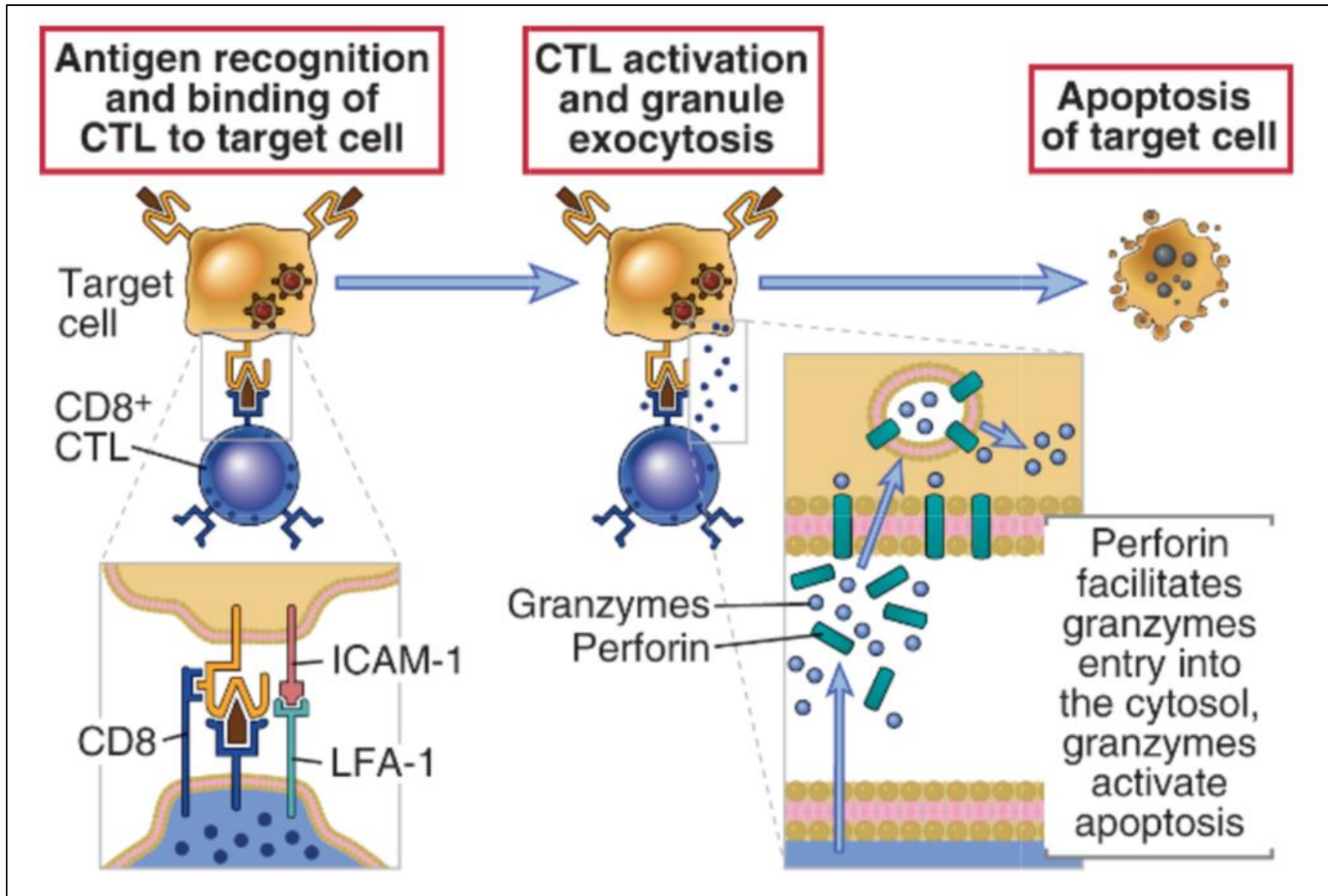
Verskillende typen T helper cel responsen



Produceren verschillende cytokines om de infectie optimaal te kunnen bestrijden



Cytotoxische T cel respons



Tumorimmunologie



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Immuunrespons tegen tumoren

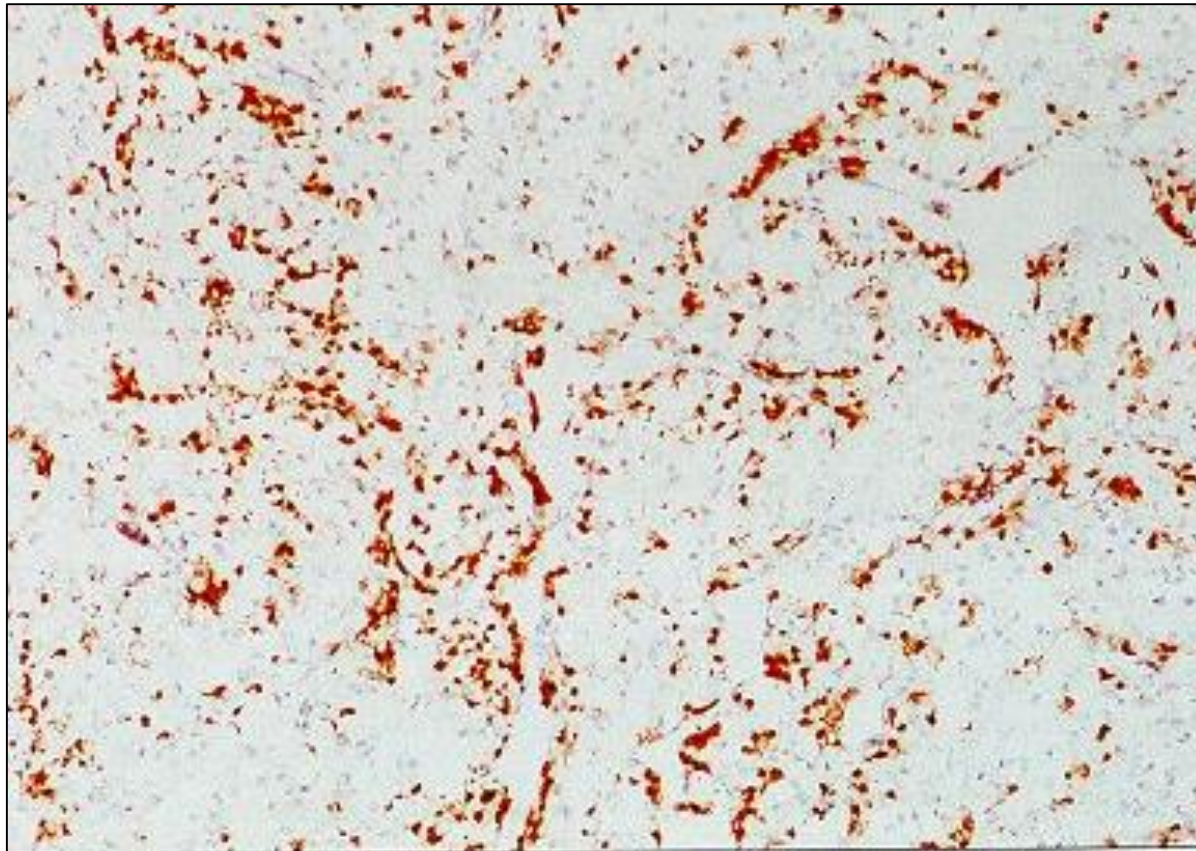


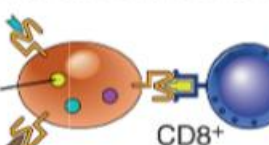
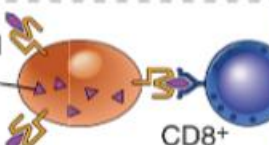
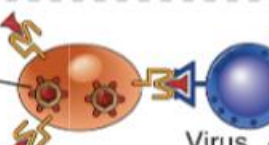


Figure 3: Histologic section of a clear cell renal cancer stained with a monoclonal antibody that recognizes the T-cell receptor (epsilon chain) on T-lymphocytes. The red staining indicates infiltration by numerous T-cells.



Welke antigenen worden herkend?

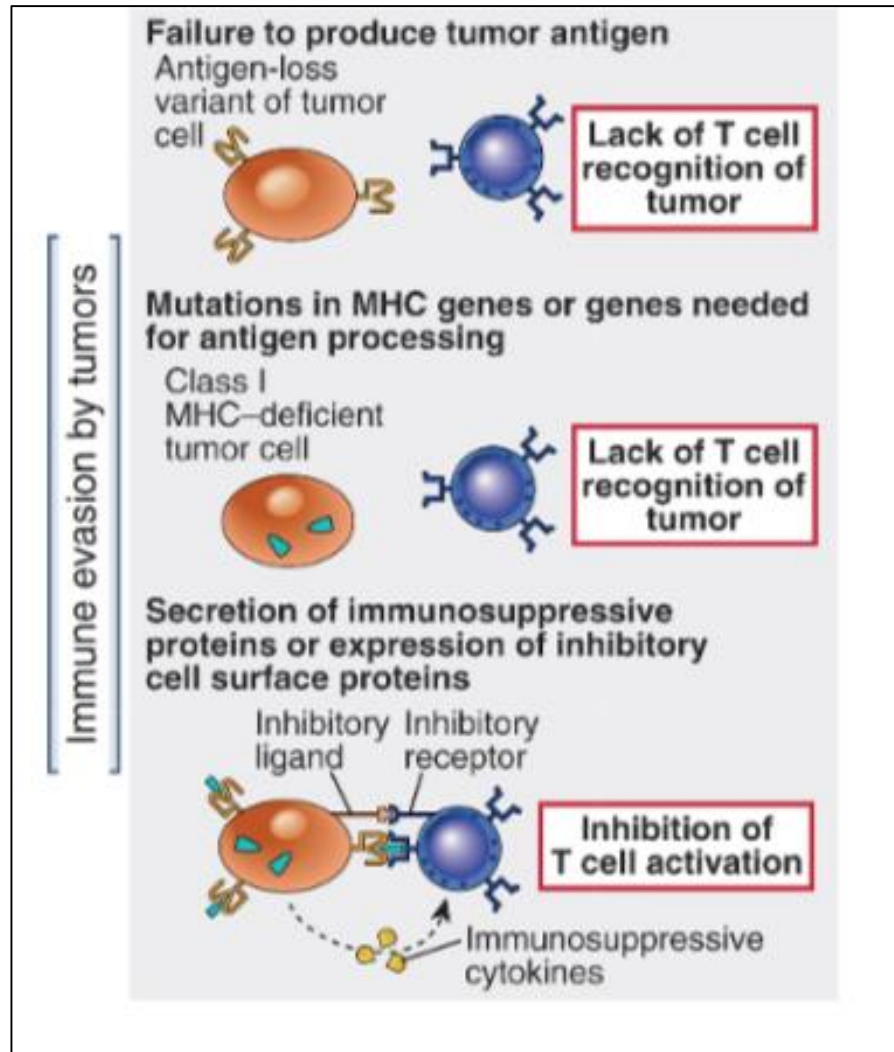
		Examples
Normal cell displaying self antigens	<p>Normal self protein</p>  <p>No T cell response</p>	
	<p>Mutated self protein that does not contribute to tumorigenesis</p> 	<p>Various mutant proteins in carcinogen or radiation-induced animal tumors and in human tumors</p>
Tumor cells expressing different types of tumor antigens	<p>Product of oncogene or mutated tumor suppressor gene</p>  <p>CD8+ CTL</p>	<p>Oncogene products: mutated Ras, Bcr/Abl fusion proteins Tumor suppressor gene products: mutated p53 protein</p>
	<p>Overexpressed or aberrantly expressed self protein</p>  <p>CD8+ CTL</p>	<p>Tyrosinase, gp100, cancer/testis antigens in various tumors</p>
	<p>Oncogenic virus</p>  <p>Virus antigen-specific CD8+ CTL</p>	<p>Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphomas</p>



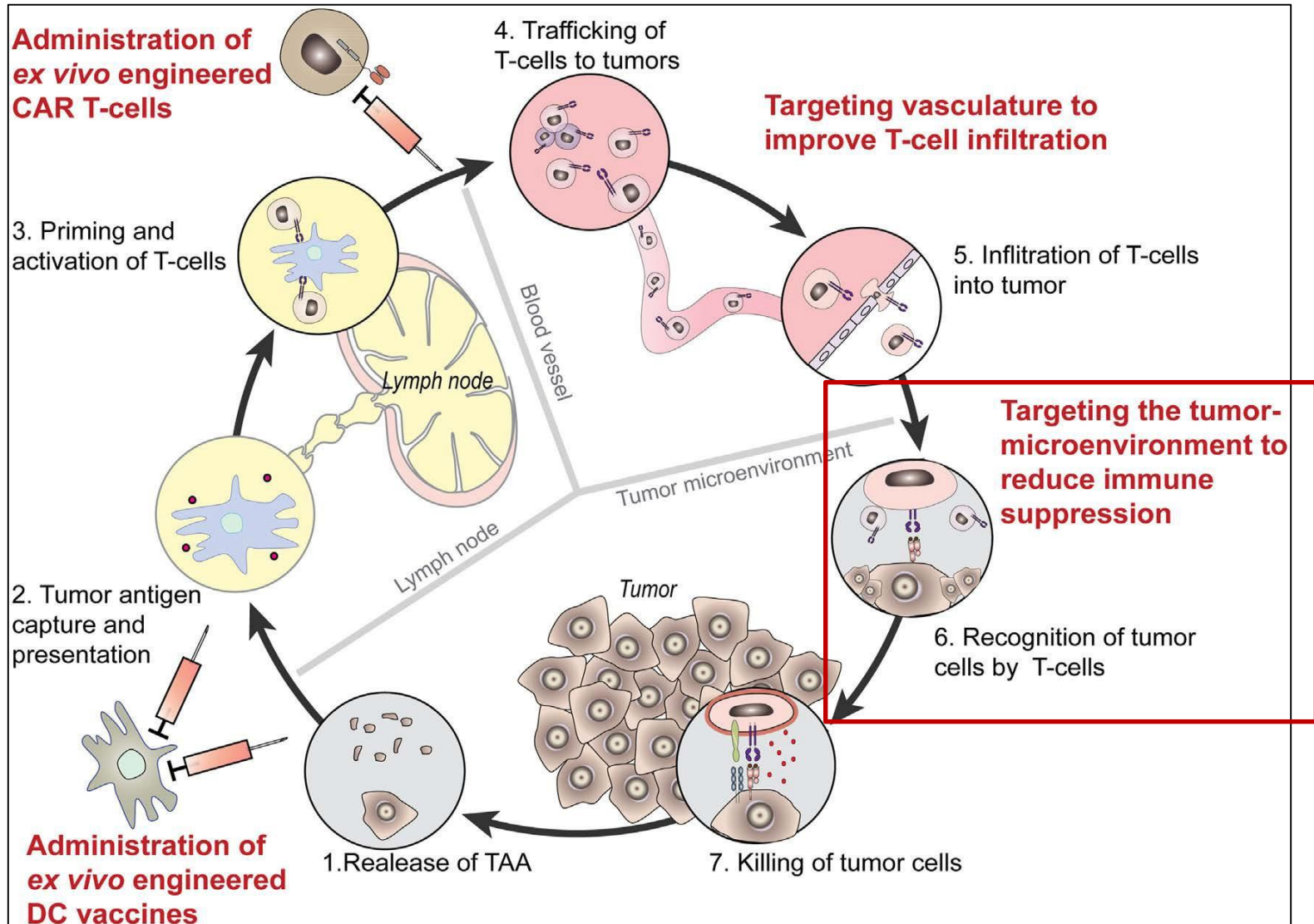
T cel respons tegen tumoren



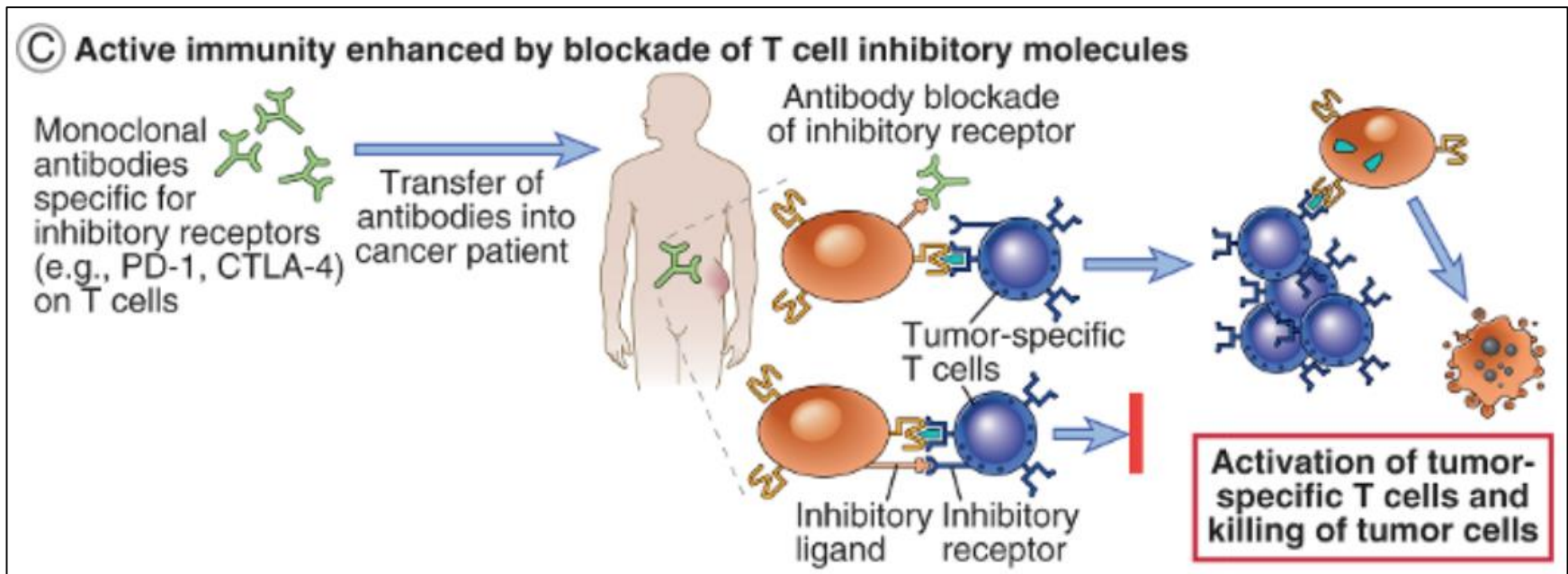
Immuunontwikijing door tumoren



"Kanker-immuniteit cyclus"



Strategieën voor immuuntherapie tegen kanker



- Ipilimumab (anti-CTLA4)
- Nivolumab (anti-PD1)



Nobelprijs 2018 (Fysiologie/Geneeskunde)



© Nobel Media AB. Photo: A. Mahmoud

James P. Allison

Prize share: 1/2

CTLA-4



© Nobel Media AB. Photo: A. Mahmoud

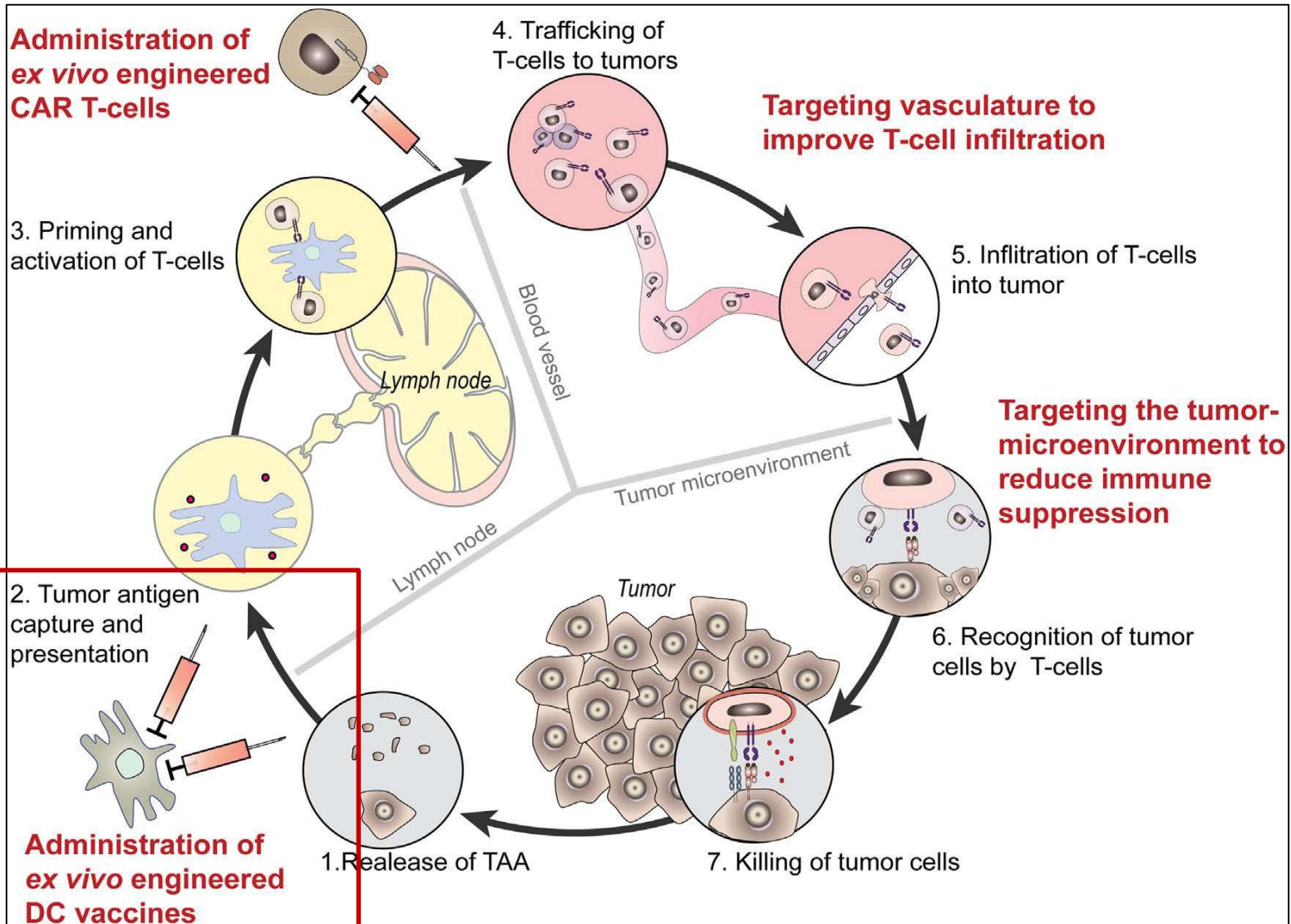
Tasuku Honjo

Prize share: 1/2

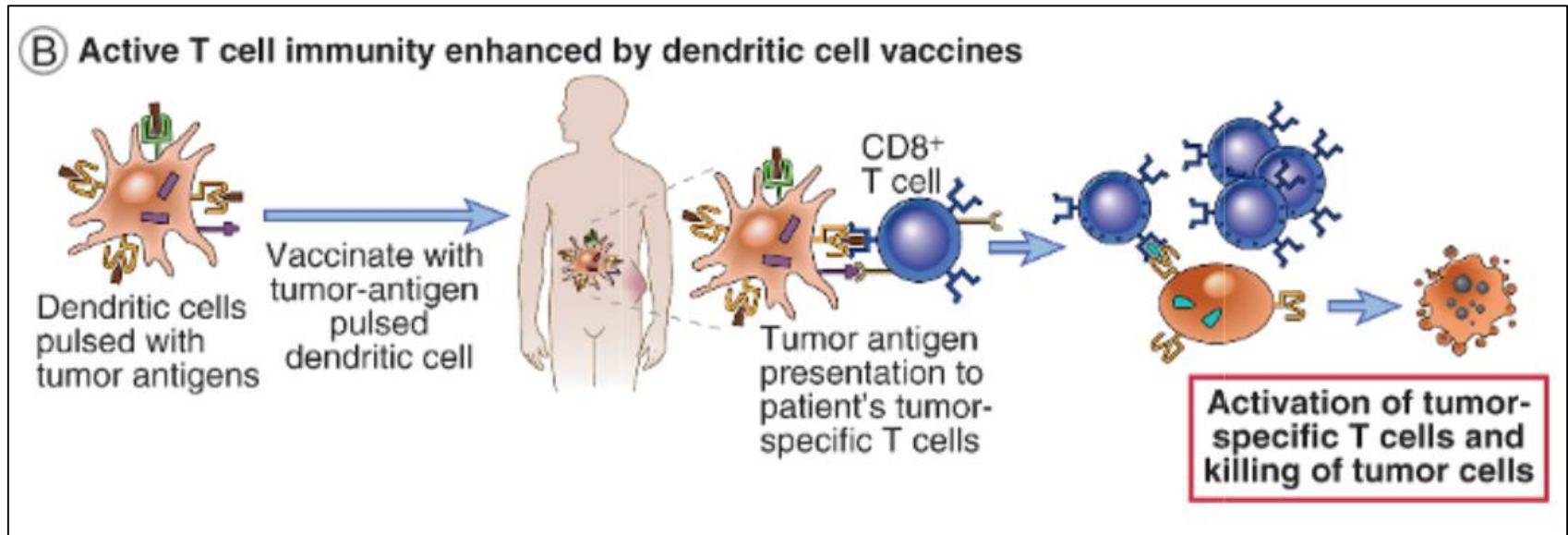
PD-1



"Kanker-immuniteit cyclus"



Strategieën voor immuuntherapie tegen kanker

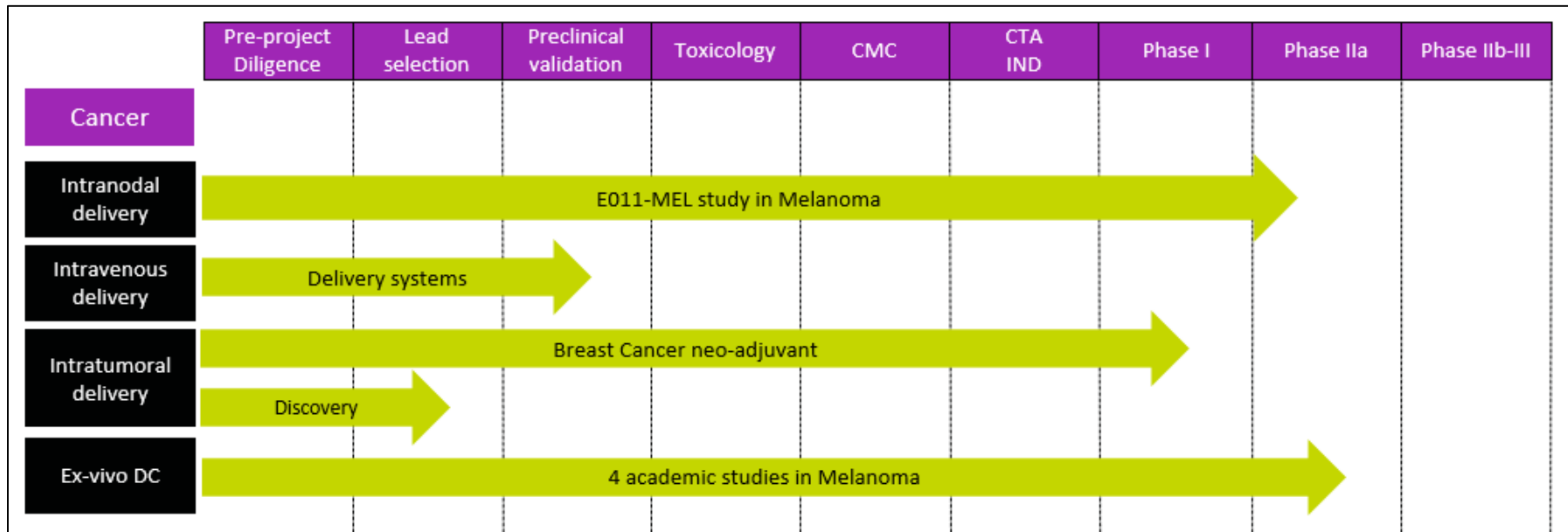


Belgisch bedrijf eTheRNA

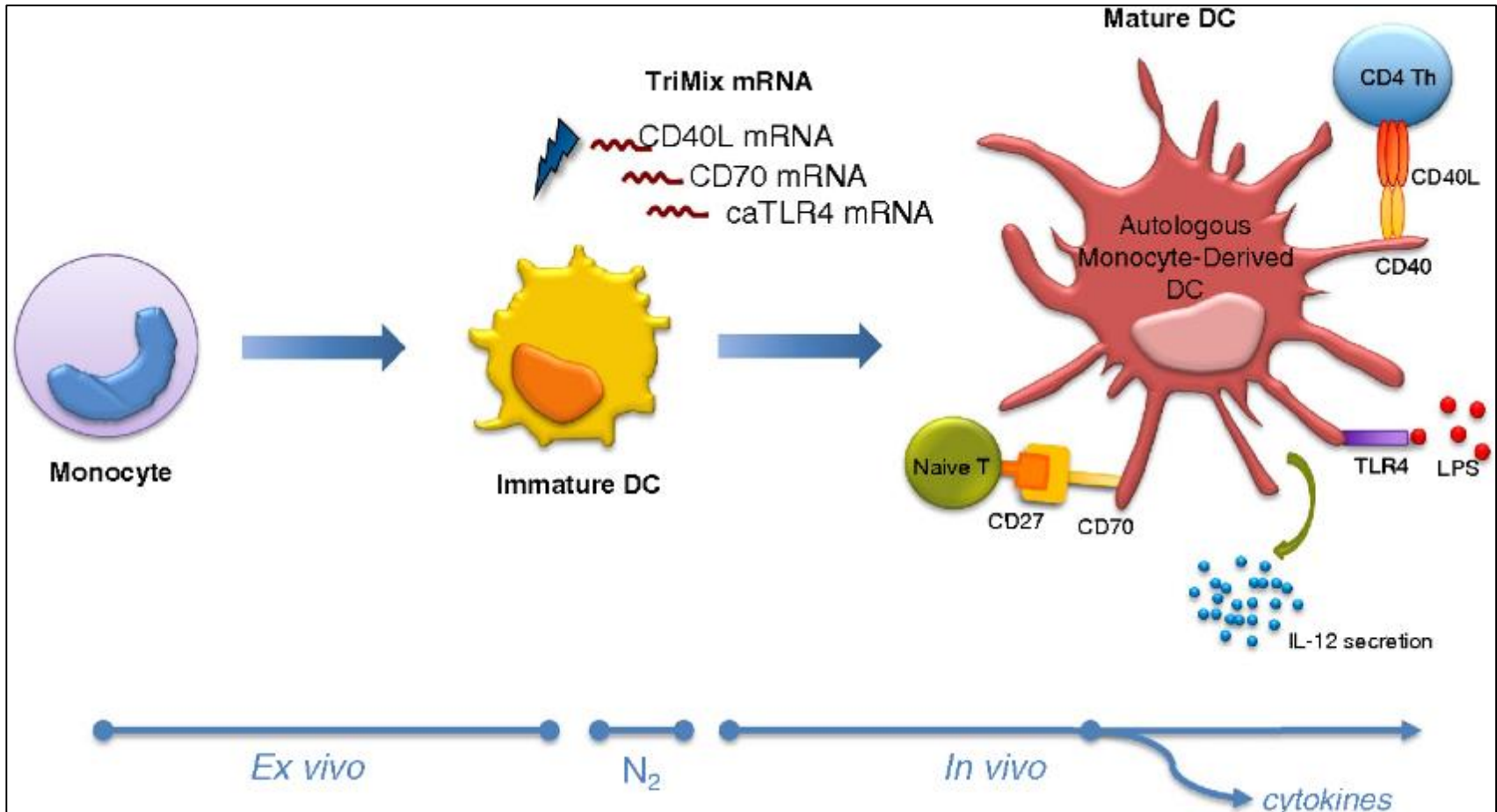


Prof. Kris Thielemans (VUB):

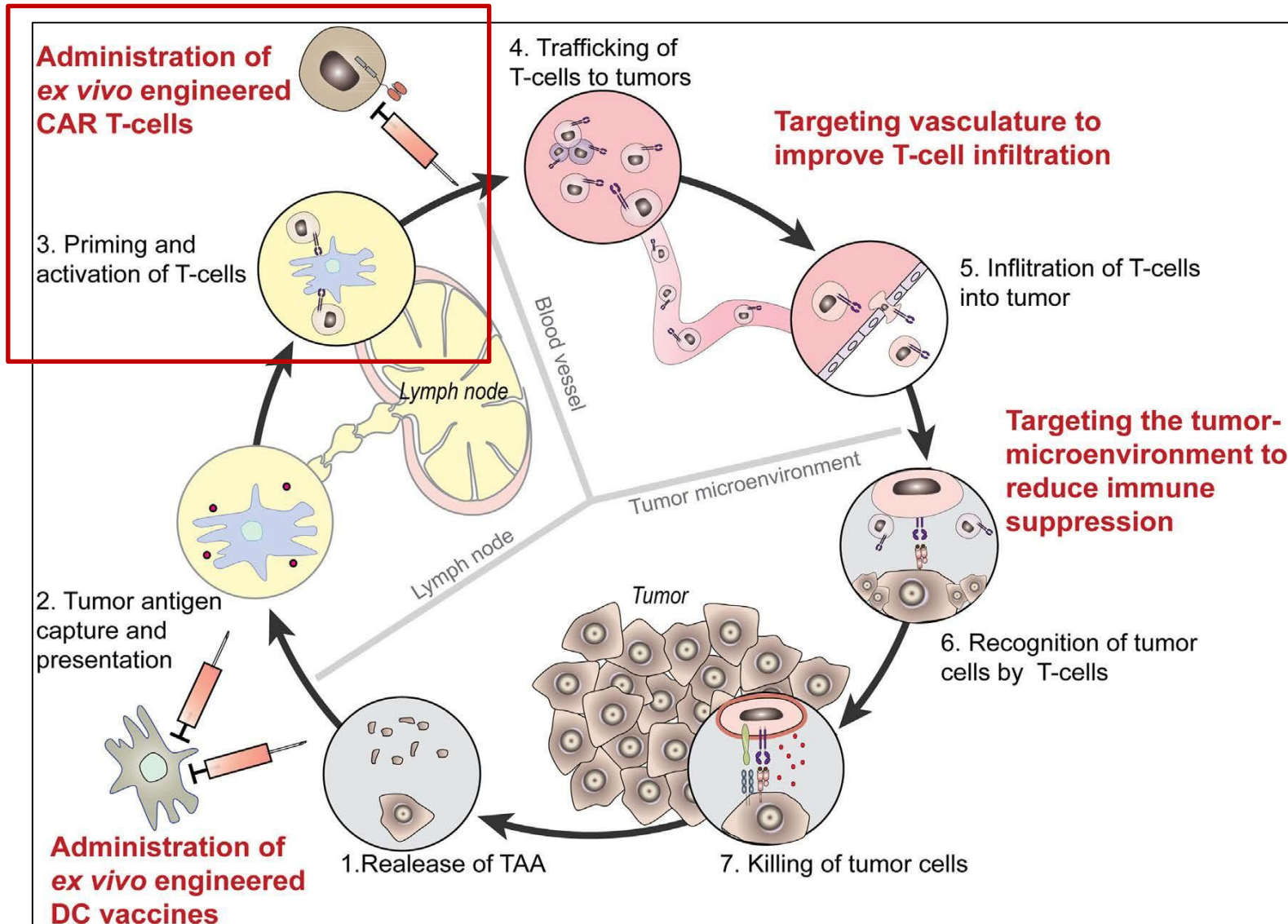
- Ontwikkelde mRNA-gebaseerd DC vaccin (“TriMix” technology)
- Creëerde spin-off eTheRNA om vaccin te testen en op de markt te brengen



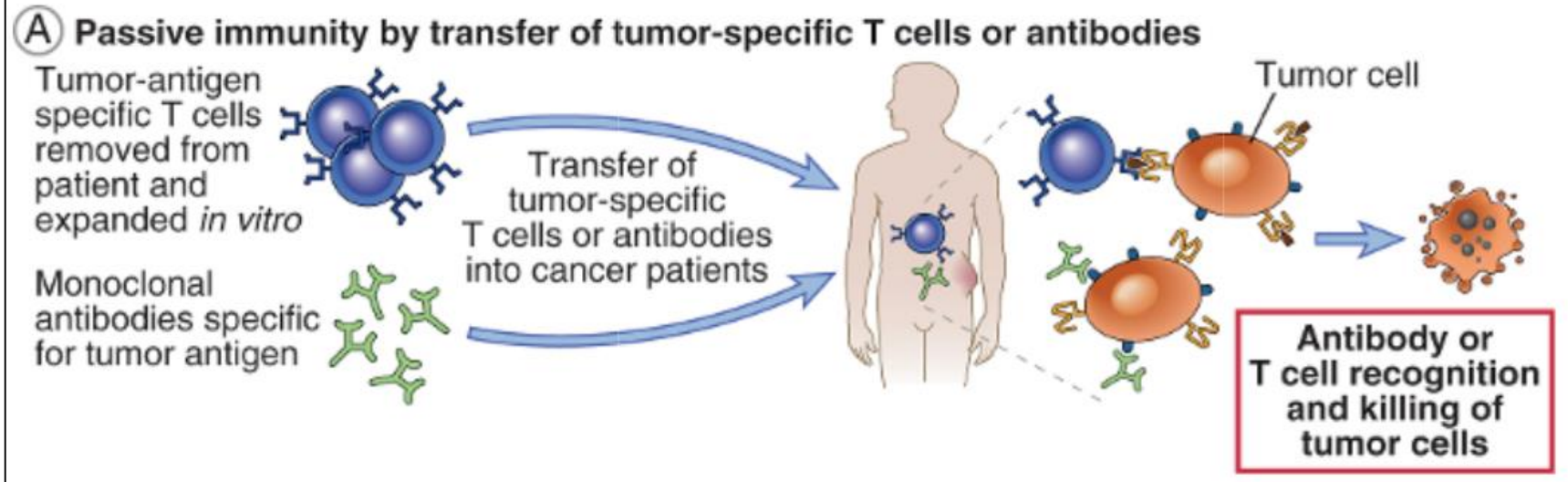
Belgisch bedrijf eTheRNA



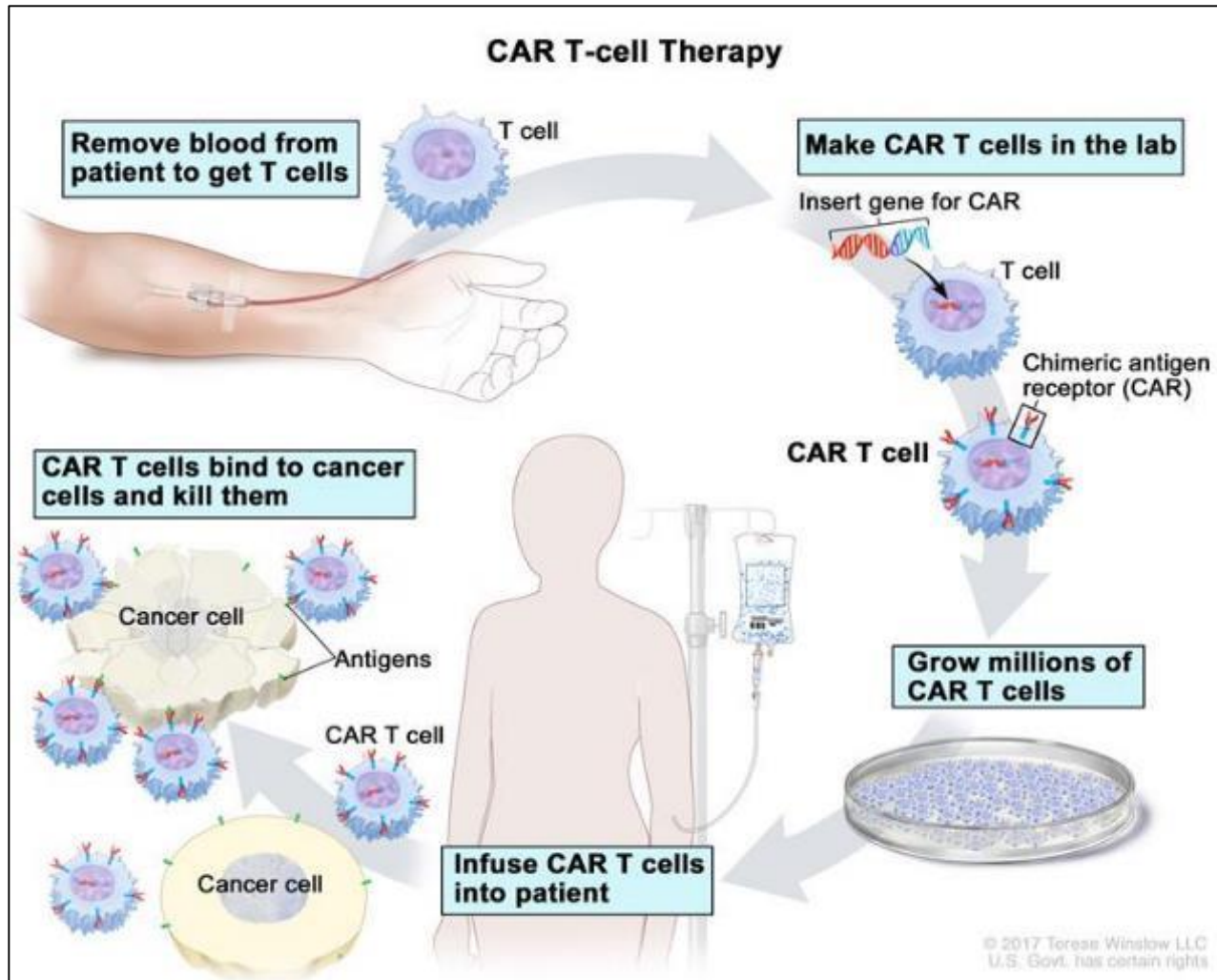
"Kanker-immuniteit cyclus"



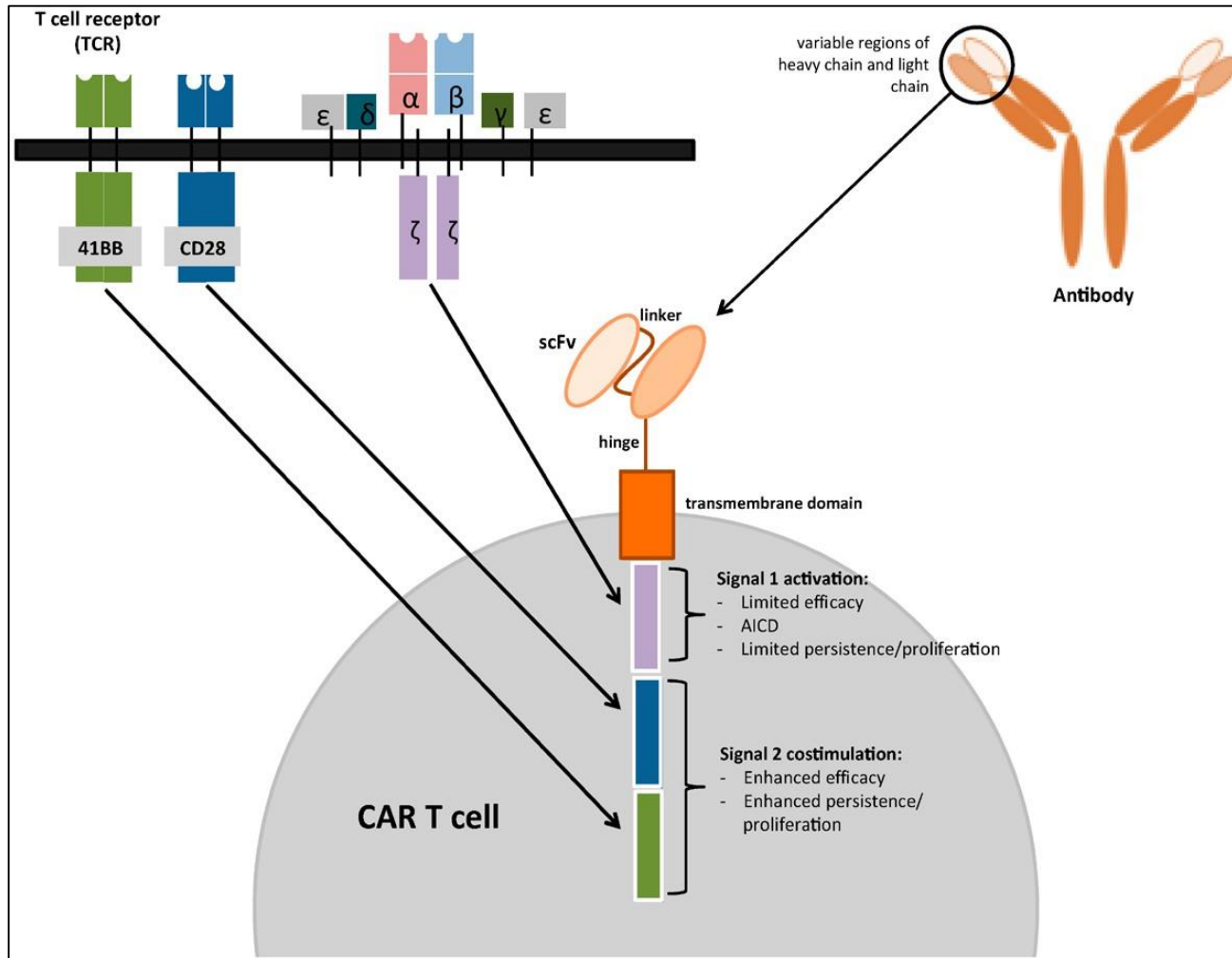
Strategieën voor immuuntherapie tegen kanker

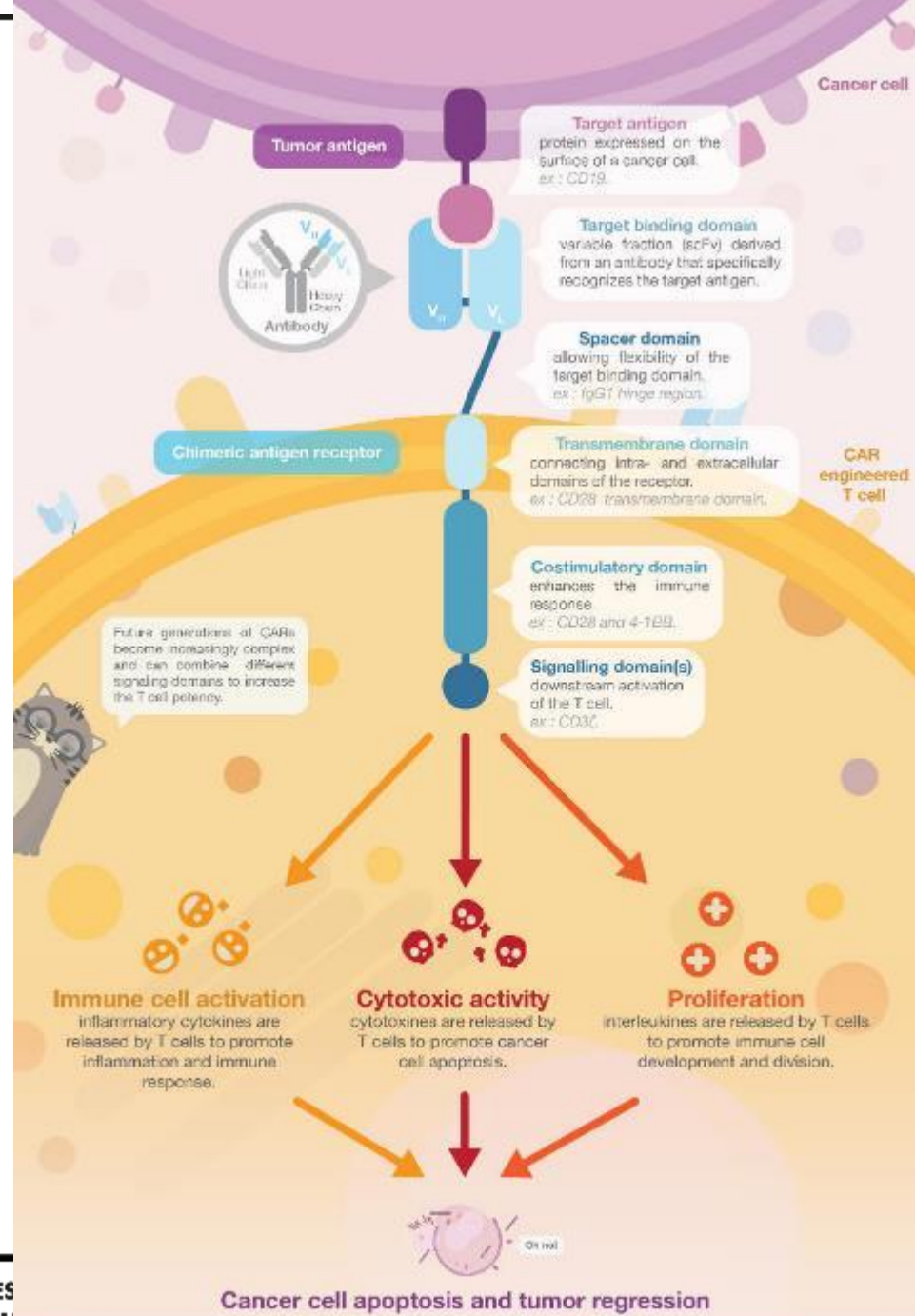


CAR-T cellen



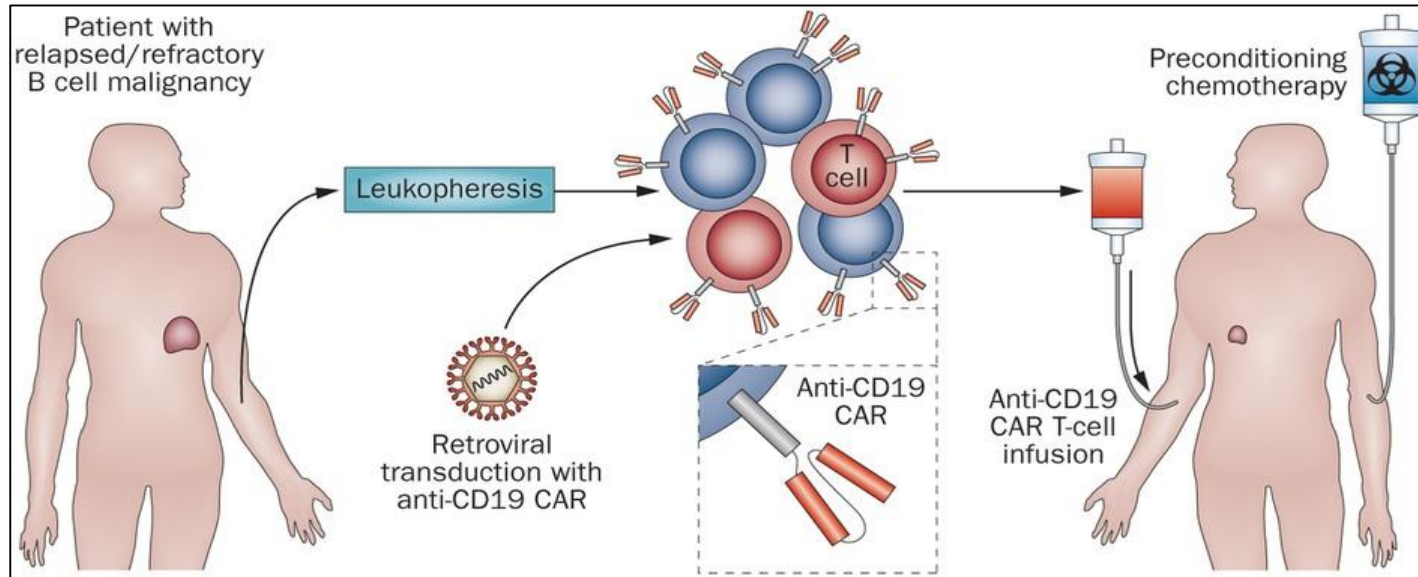
CAR-T cellen





CAR-T cellen

- Succesverhaal: B-cel leukemie
- CAR-T cellen gericht tegen CD19 (oppervlaktemolecule op B-cellen)



- Sinds 1 juni 2019 terugbetaald (€400.000!)



Auto-immuniteit



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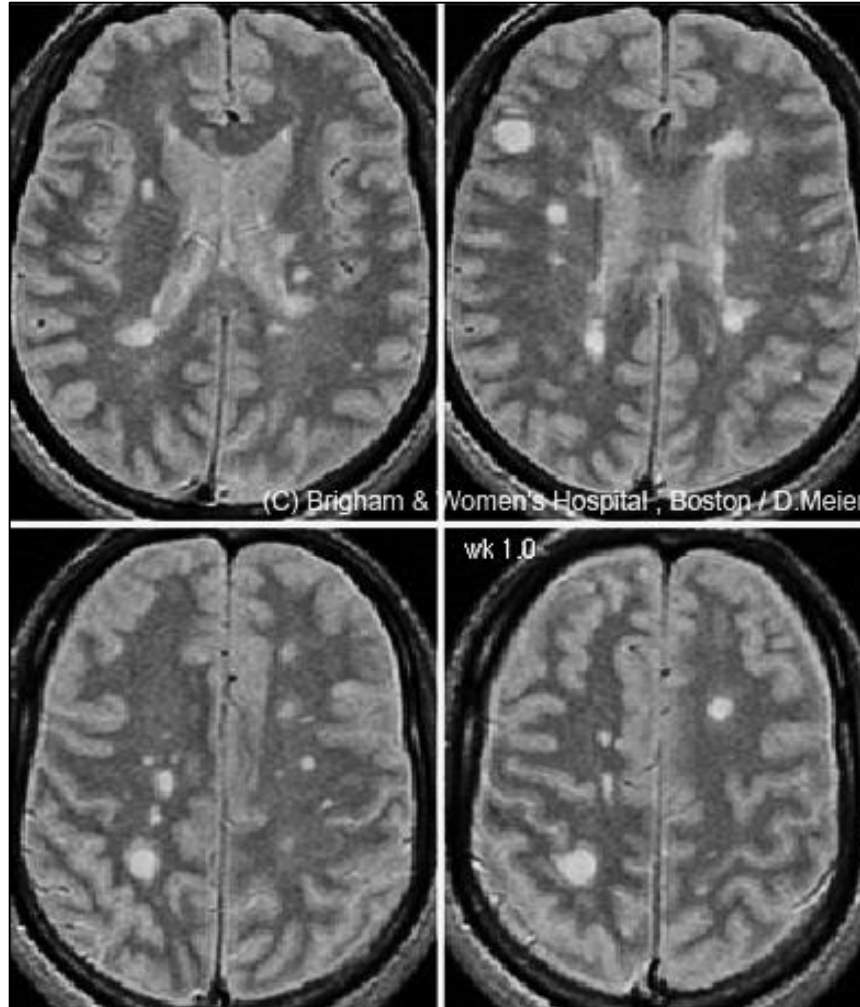
“Schoolvoorbeeld”: multiple sclerose



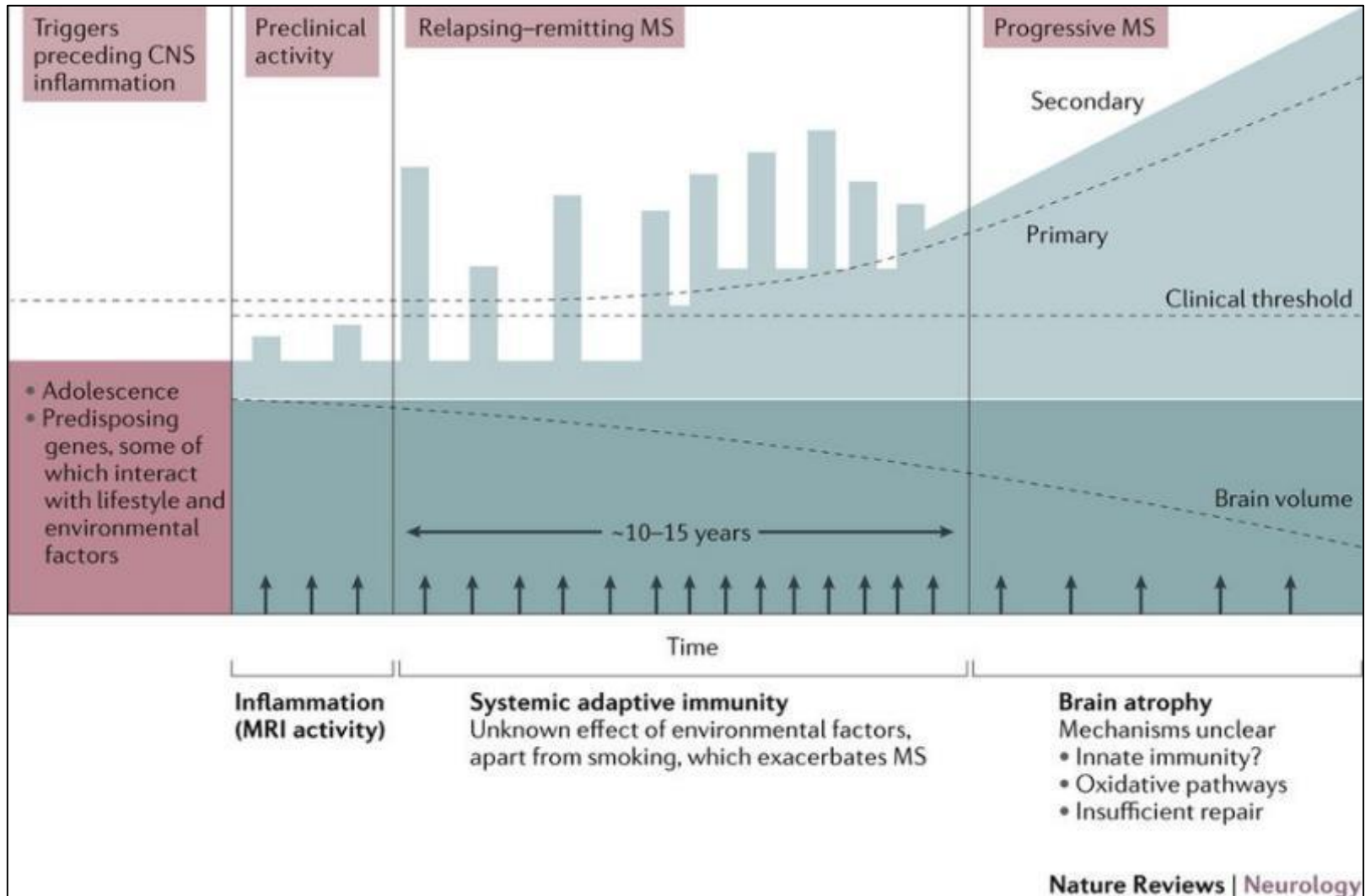
Multiple sclerose



Immuunrespons tegen eigen lichaam

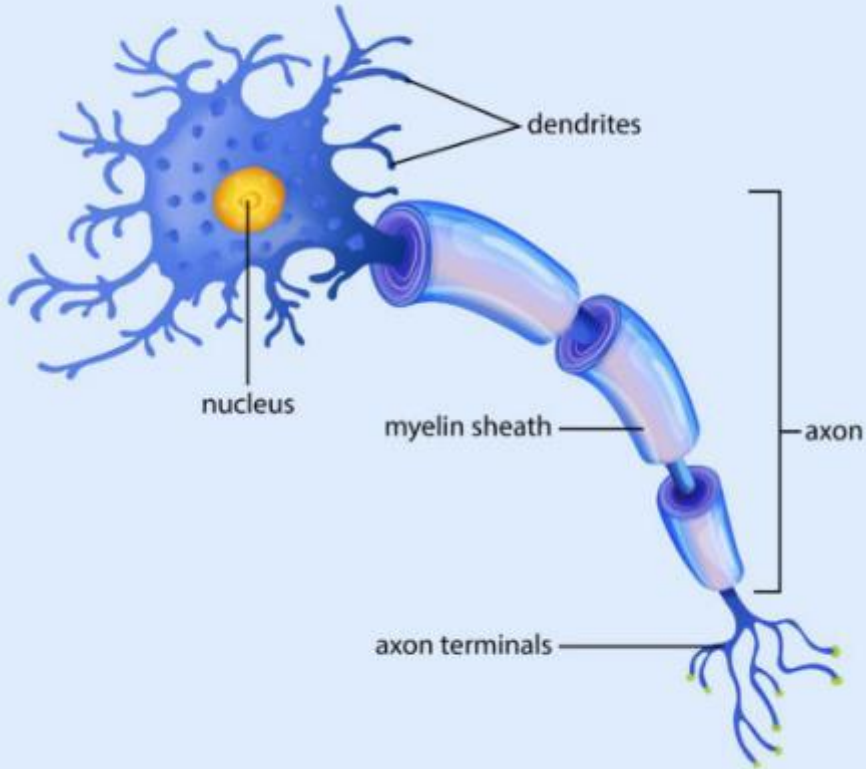


Multiple sclerose: ziekteverloop

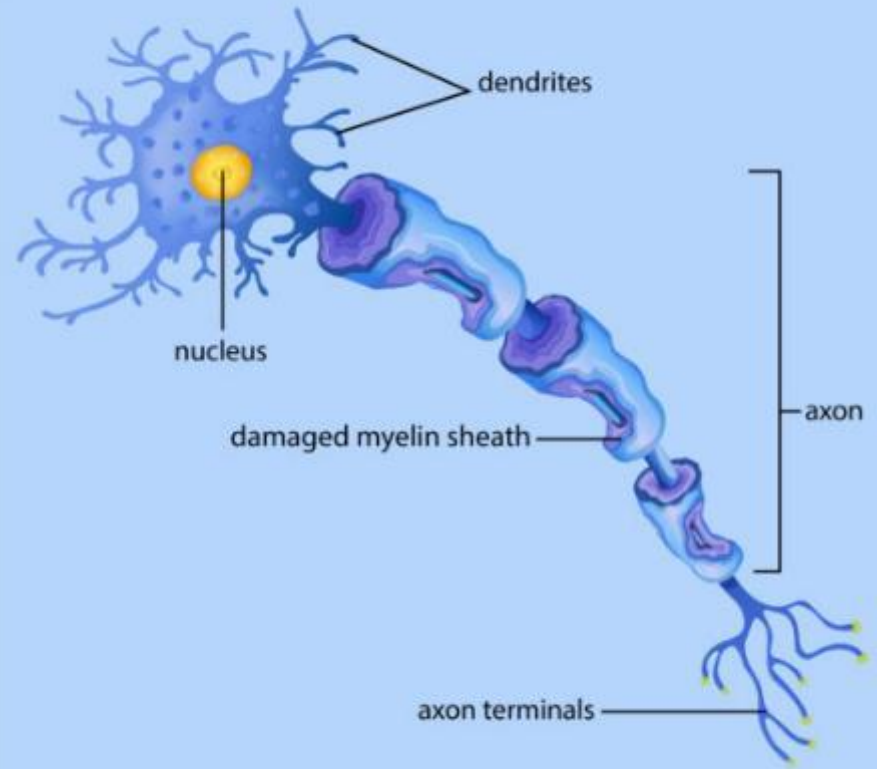


Multiple sclerose: aanval tegen myeline

Normal Nerve



Multiple Sclerosis

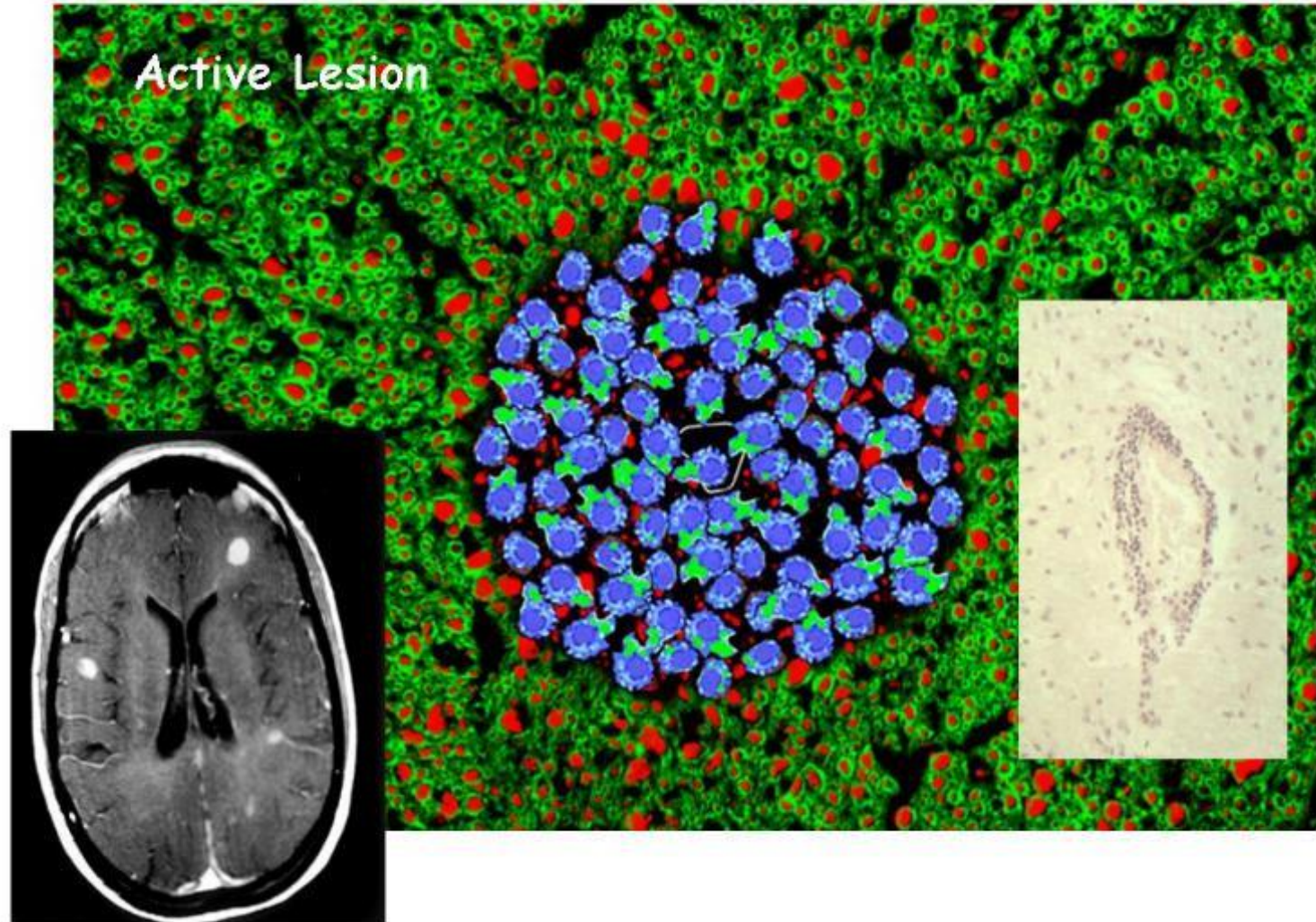


Multiple sclerosis: lesies in de hersenen



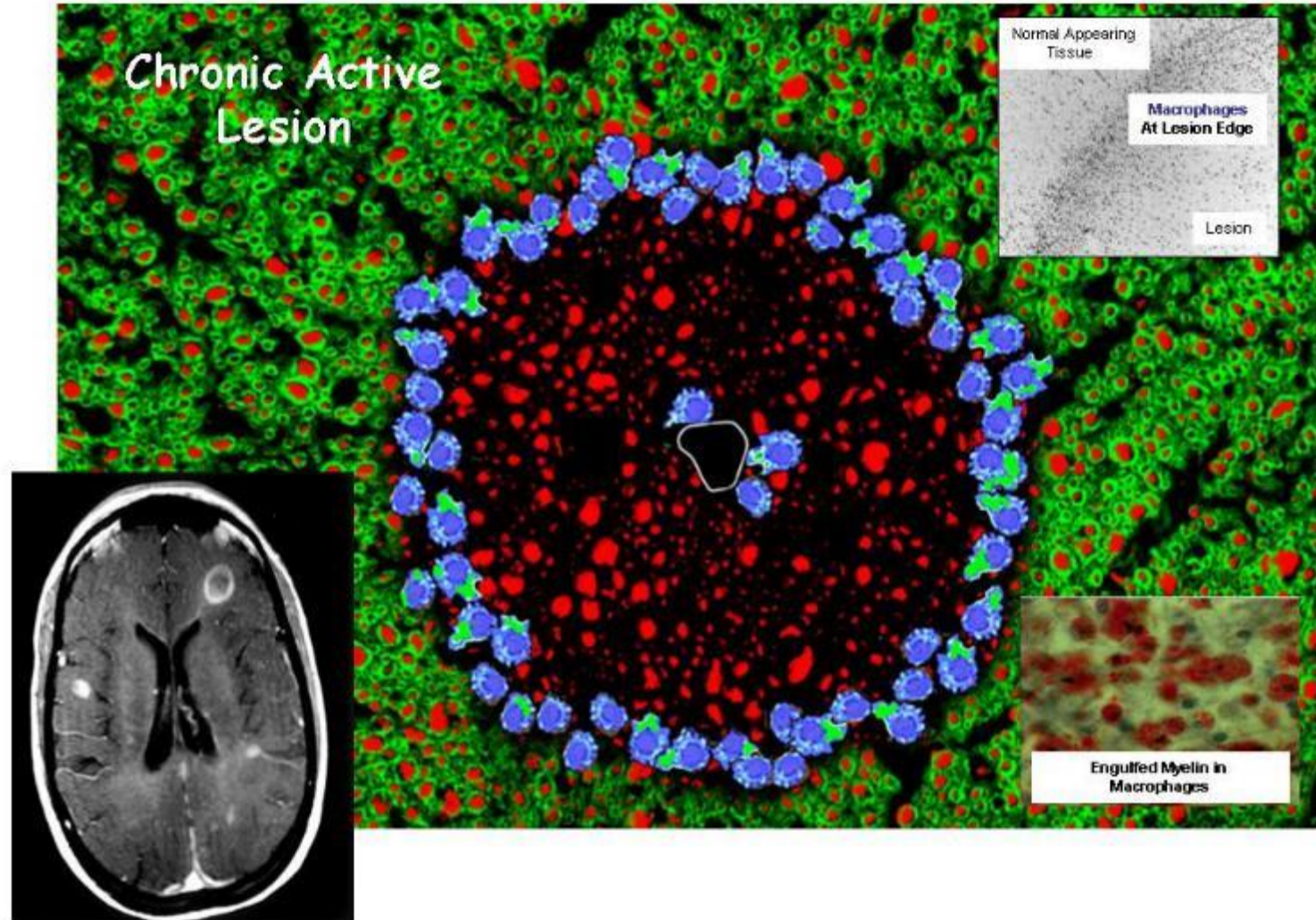
Multiple sclerosis: lesies in de hersenen

MULTIPLE SCLEROSIS LESION



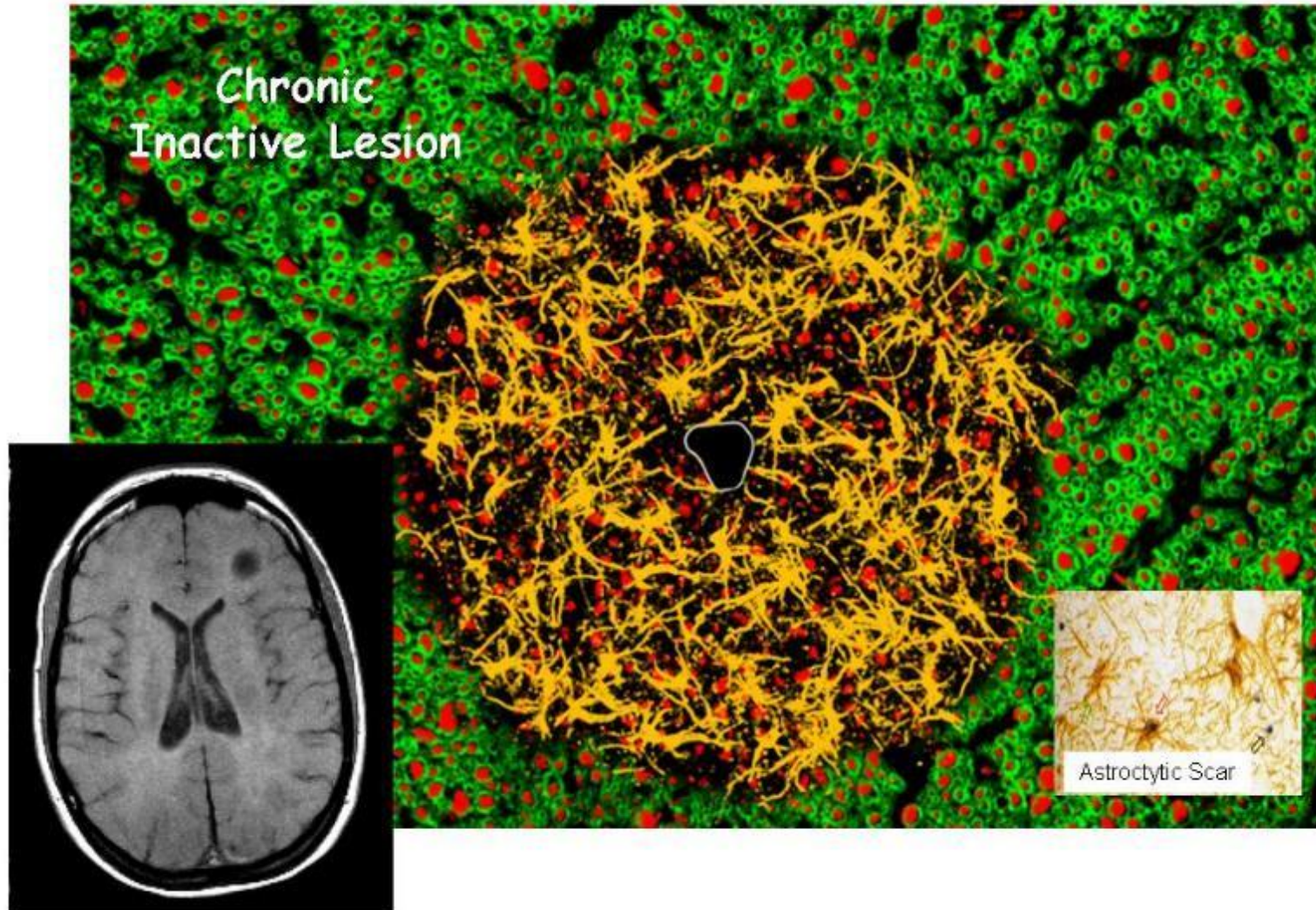
Multiple sclerosis: lesies in de hersenen

MULTIPLE SCLEROSIS LESION



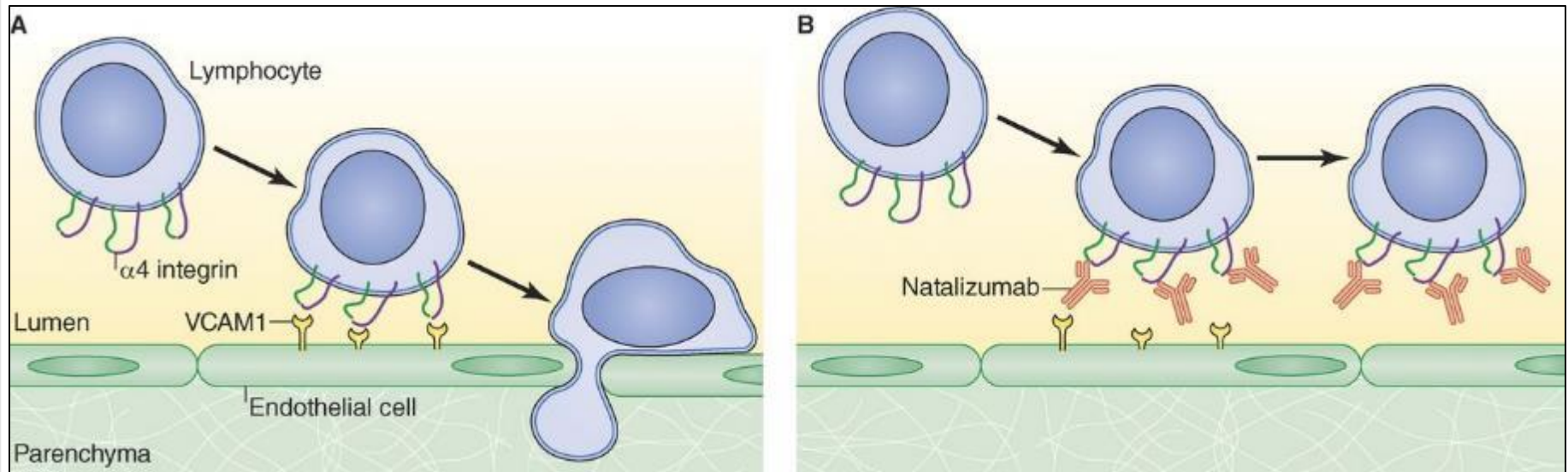
Multiple sclerosis: lesies in de hersenen

MULTIPLE SCLEROSIS LESION



Antilichaamtherapieën

- Natalizumab (anti- α 4 integrine):
 - Blokkeert infiltratie van immuuncellen in de hersenen
 - Mogelijk levensbedreigende complicatie: PML

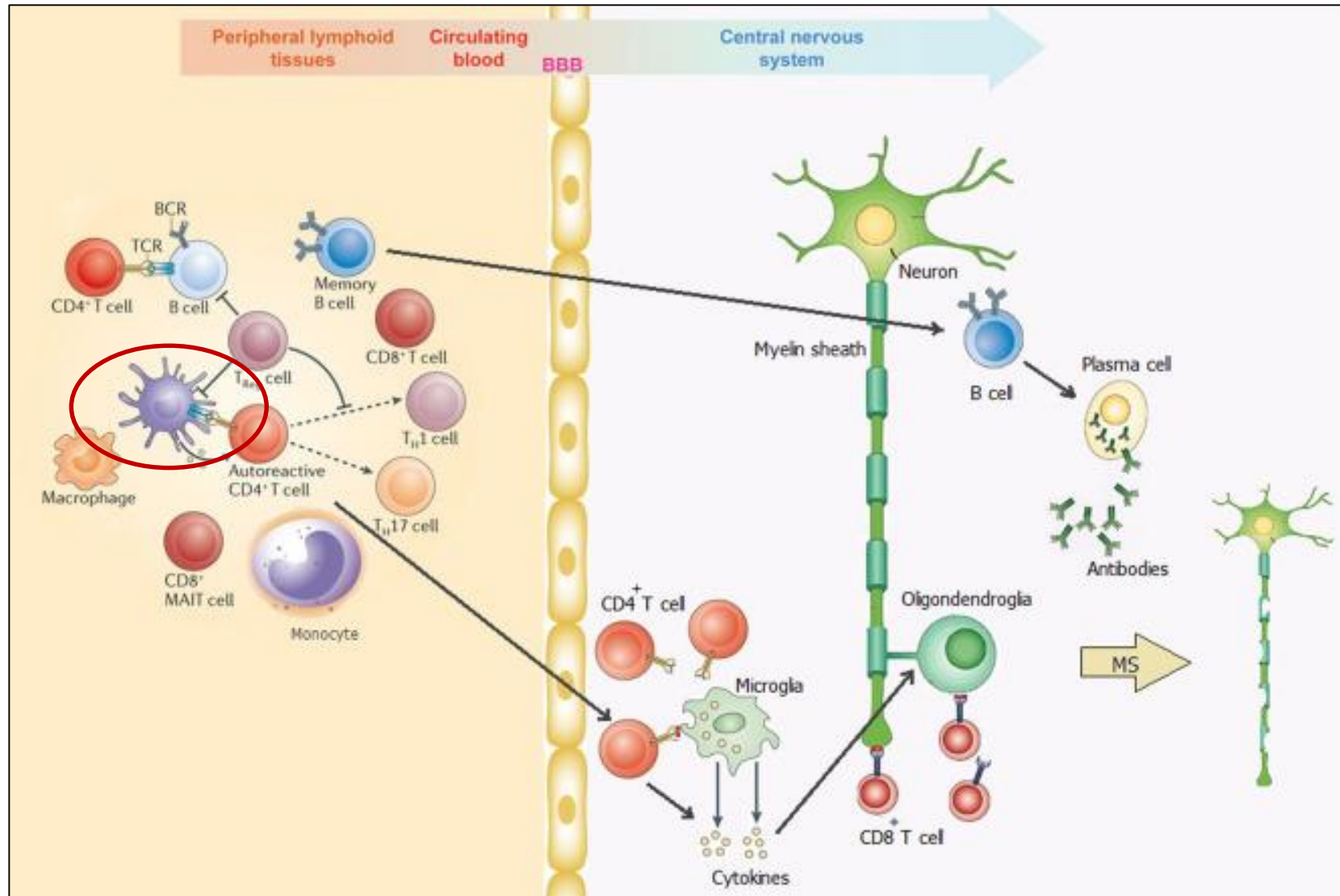


Antilichaamtherapieën

- Ocrelizumab (anti-CD20):
 - Doodt B-cellen (immuunsuppressief)
 - Eerste goedgekeurde therapie voor primair progressieve MS
- Alemtuzumab (anti-CD52):
 - Doodt lymfocyten (sterk immuunsuppressief)
 - Patiënten ontwikkelen secundaire autoimmunititeit
- Daclizumab (anti-CD25):
 - Blokkeert activatie van T-cellen



Immuunrespons op celniveau



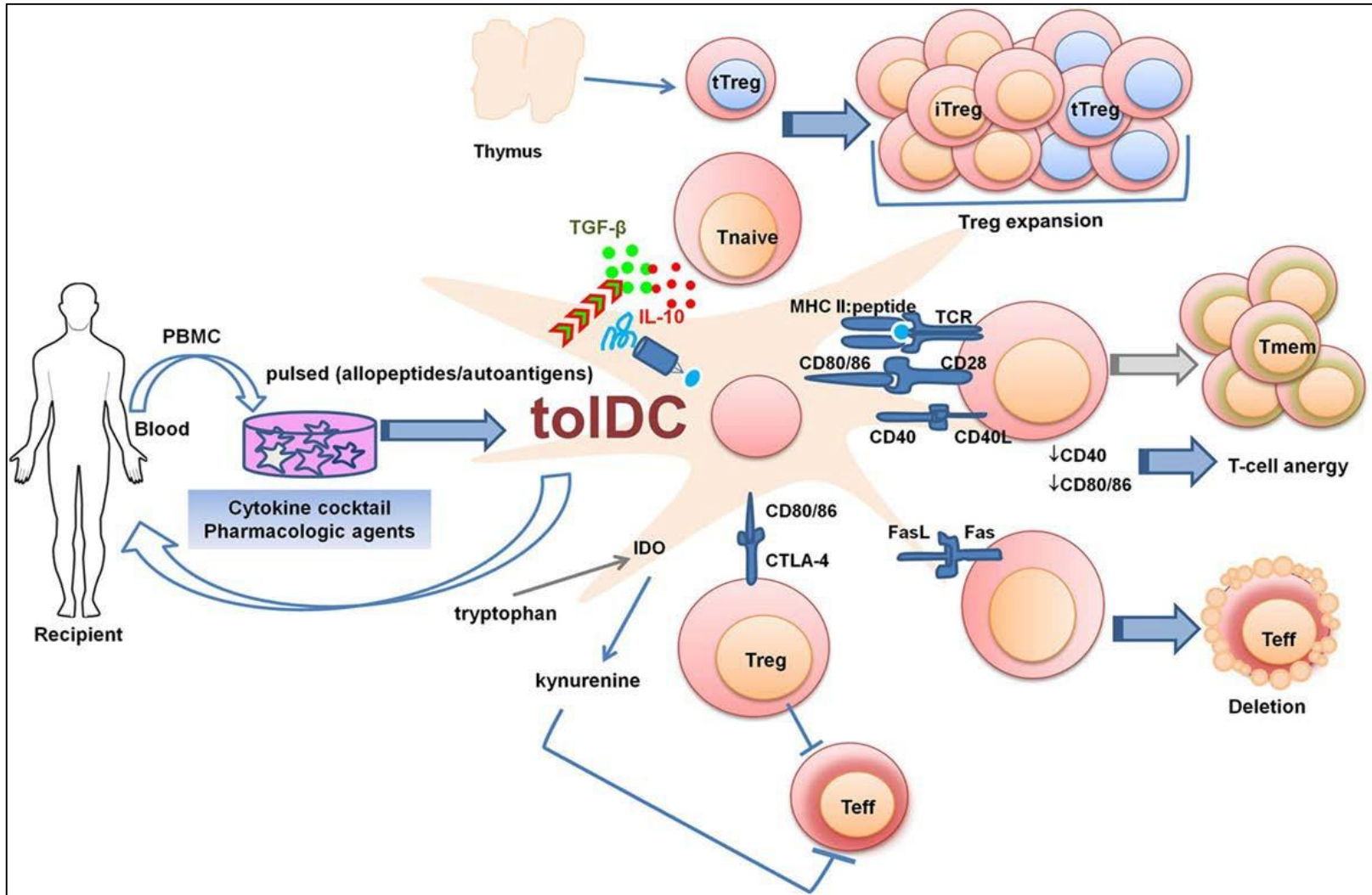
Celtherapie: toIDC

NCT identifier	Phase	Therapeutic agent	Status	Sponsor/collaborators	Disease
NCT00445913	I	Autologous dendritic cell (DC)	completed	University of Pittsburgh	T1DM
NCT02354911	II	Autologous immunoregulatory DC	Not yet recruiting	DiaVacs, Inc., and others	T1DM
NCT01947569	I/II	Autologous co-stimulation-impaired DC	Unknown	DiaVacs, Inc.	T1DM
NCT00434850	II	Deoxyspergualin, an immunosuppressant drug, shown to modulate DC differentiation and function	Completed	NIAID and NIDDK	Islets transplantation in T1DM
NCT01352858	I	Autologous toIDC	Unknown	Newcastle University and Arthritis Research UK	Rheumatoid arthritis (RA)
NCT00279461	II	Vit D3	Withdrawn	Indiana University	RA
NCT02283671	I	toIDCs loaded with myelin peptides	Currently recruiting	Sara Varea	Multiple Sclerosis (MS) and Neuromyelitis Optica
NCT02618902	I	toIDCs	Not yet recruiting	University Hospital, Antwerp	MS
NCT02903537	I	Autologous tolerogenic modDCs loaded with a pool of myelin peptides (toIDC-VitD3)	Not yet recruiting	Fundació Institut Germans Trias i Pujol	MS
NCT02622763	I	Intralesional administration of toIDCs	Currently recruiting	Fundacion Clinic per a la Recerca Biomédica	Crohn's Disease
NCT02252055	I/II	Autologous toIDCs	Currently recruiting	Nantes University Hospital	Kidney transplantation

NP, not provided; T1DM, type 1 diabetes mellitus; NIAID, National Institute of Allergy and Infectious Diseases; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases.



Celtherapie: toIDC



Celtherapie: toIDC

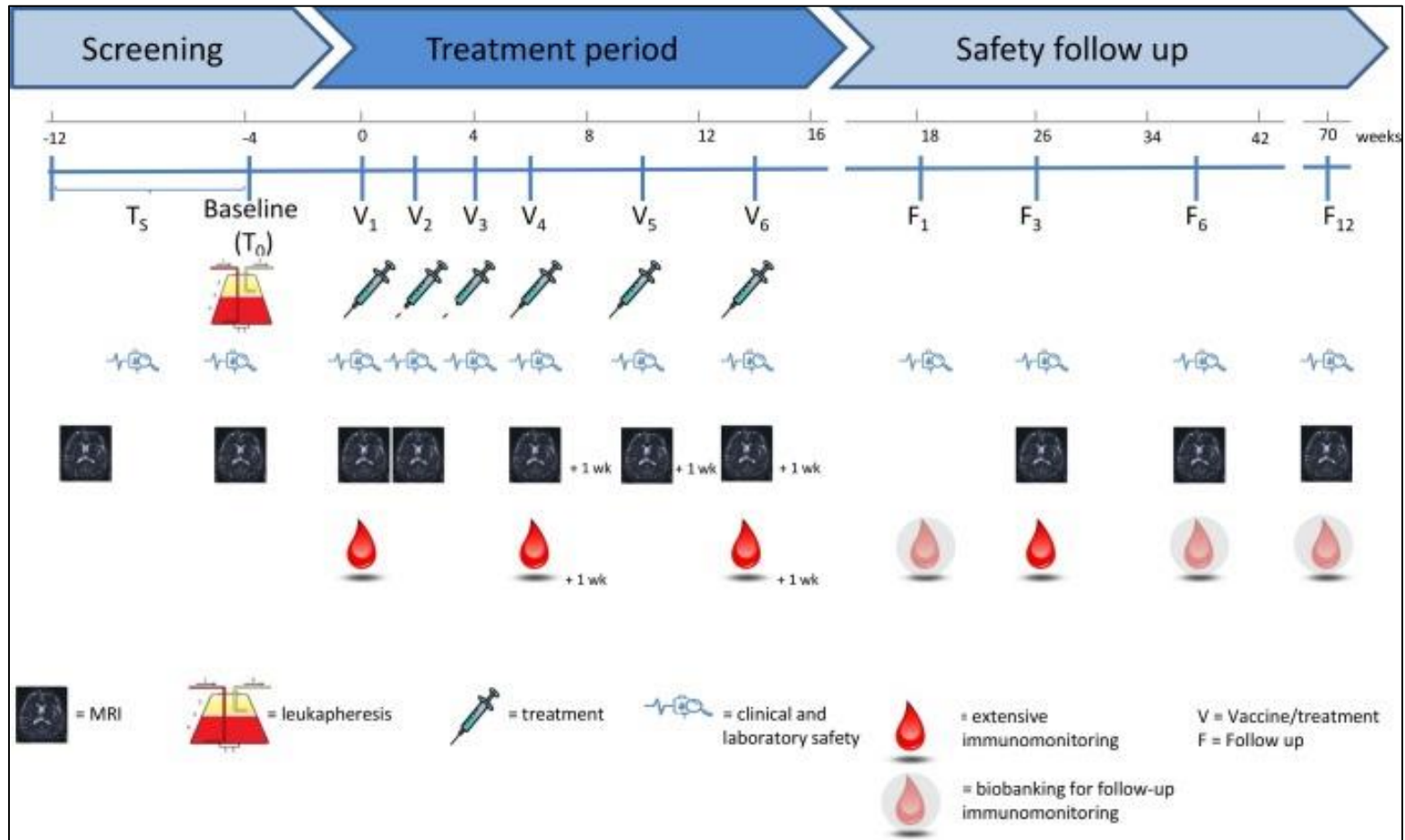


Prof. Nathalie Cools (UA):

- Ontwikkelde toIDC therapie voor MS
- Startte Anicells: een accelerator om onderzoek naar en ontwikkeling van celtherapie te verbeteren



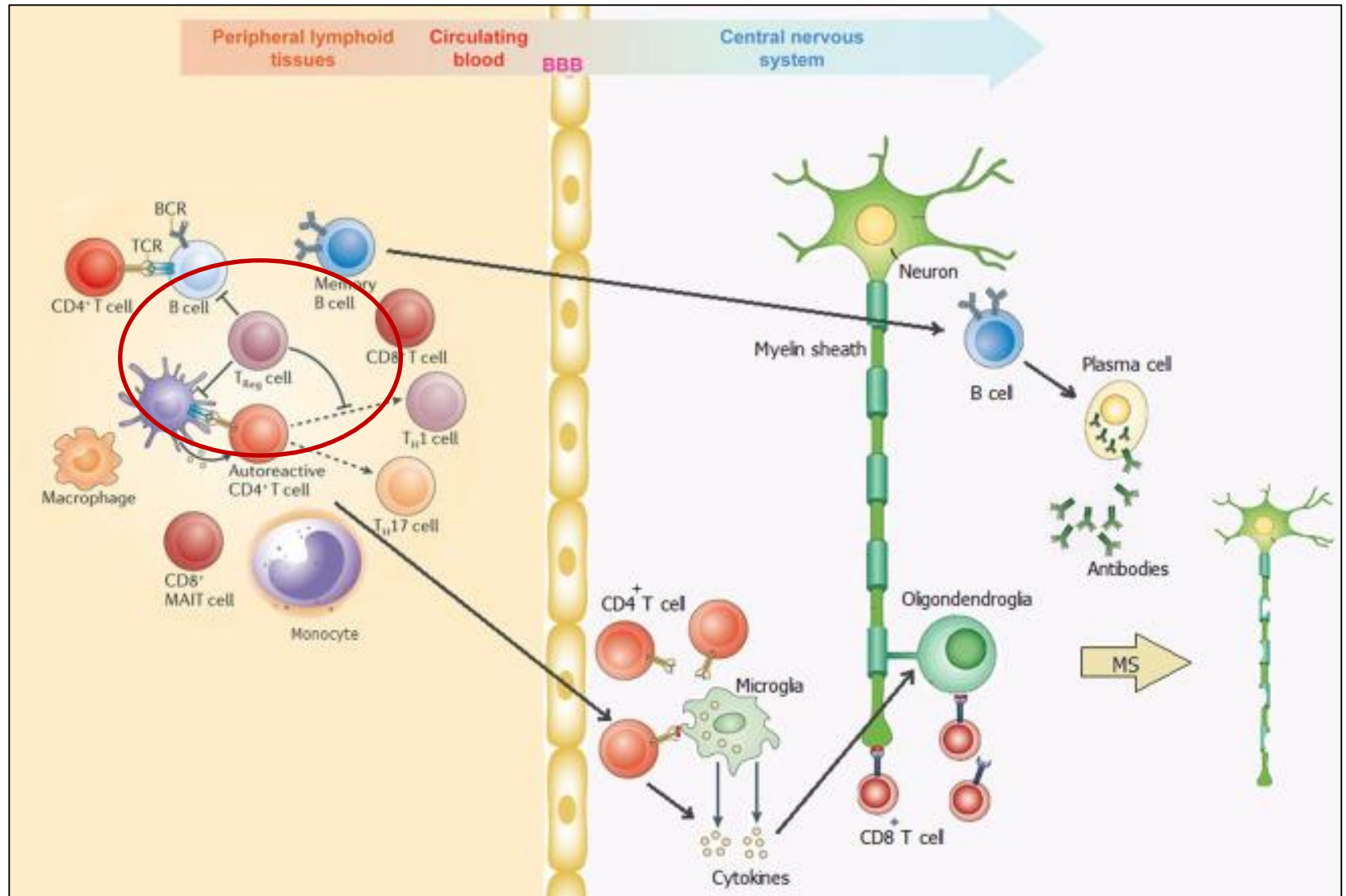
Celtherapie: toIDC



Eerste resultaten: vaccin wordt goed verdragen en blijkt veilig te zijn



Immuunrespons op celniveau



Celtherapie: Tregs

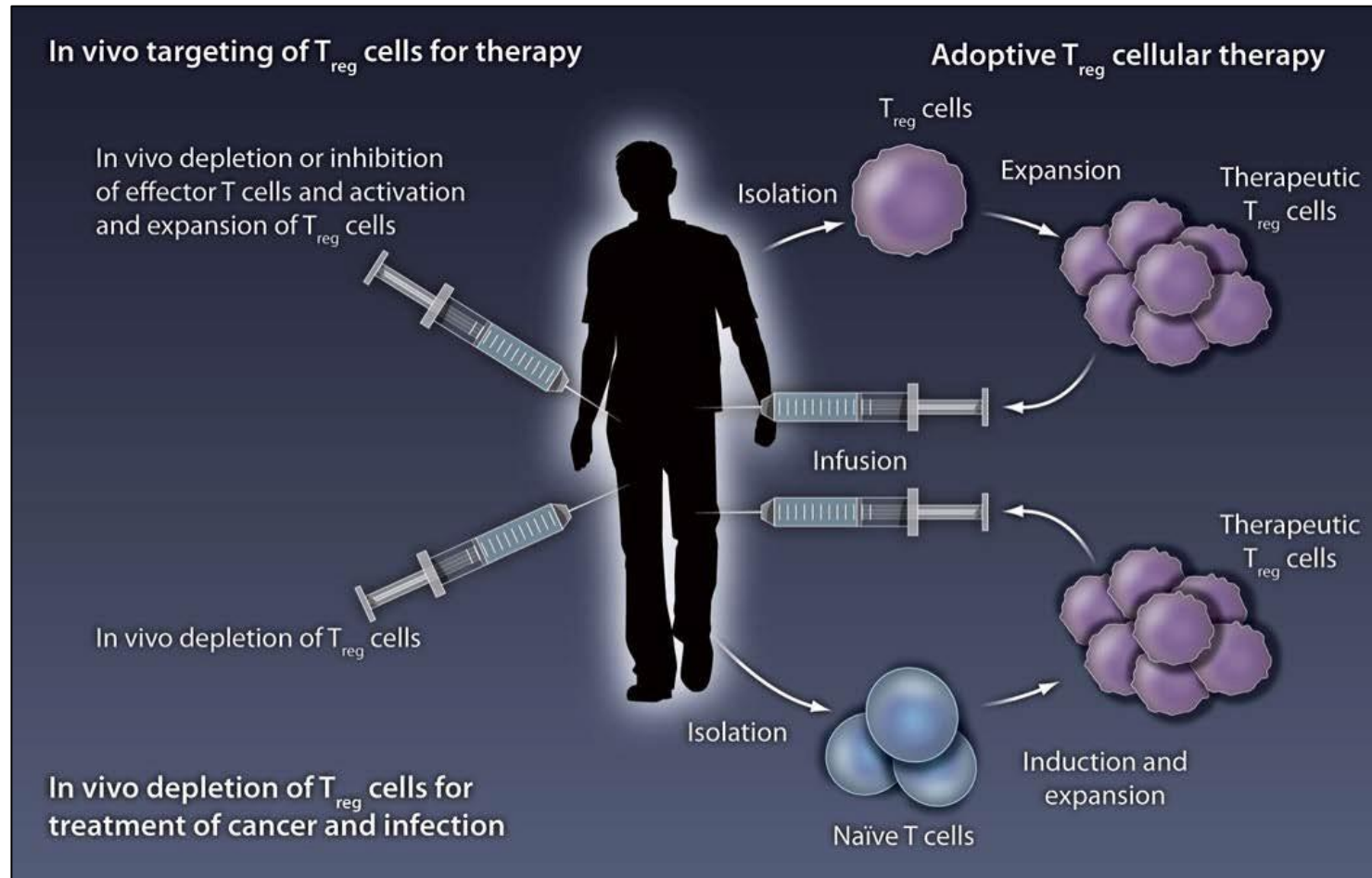
Table 1 continued

Study ID	Phase	Product	Indication	Effects	Centre	Source
TregSM; EudraCT: 2014-004320-22	I	Expanded poly-tTregs	Multiple sclerosis	Recruiting	Gdansk	[51]
NCT02704338	I	Expanded poly-tTregs	Autoimmune hepatitis	Not yet recruiting	Nanjing	[71]
NCT02772679	II	Expanded poly-tTregs with IL2	Recent T1DM	Recruiting	San Francisco	[71]
NCT02428309	II	Expanded poly-tTregs	Systemic lupus erythematosus	Recruiting	San Francisco	[71]
NCT02932826	I	Expanded third-party CB poly-Tregs	Recent T1DM	Recruiting	Hunan	[71]
NCT03011021	I	Expanded third-party CB poly-Tregs and liraglutide	Recent T1DM	Recruiting	Hunan	[71]
T-Rex study; NCT02691247	II	Expanded poly-tTregs	Recent T1DM	Recruiting	San Francisco, Aurora, New Haven, Gainesville, Miami, Indianapolis, Boston, Fargo, Kansas City, Portland, Sioux Falls, Nashville	[71]
Other						
NCT03101423	I	Donor poly-Tregs DLI	Beta thalassemia major	Recruiting	Nanning	[71]

CB cord blood, *CNI* calcineurin inhibitor, *DLI* donor lymphocyte infusion, *GvHD* graft vs. host disease, *HSCT* hematopoietic stem cell transplantation, *IL* interleukin, *poly-Tregs* polyclonal T regulatory cells, *poly-tTregs* polyclonal thymus-derived T regulatory cells, *T1DM* type 1 diabetes mellitus, *Tconv* T conventional cells



Celtherapie: Tregs



Samenvatting

- Immuunsysteem verstoord in kanker en auto-immuniteit
- Gebruik maken van immuunsysteem voor therapie:
 - Antilichaamtherapie
 - Celtherapie

→ Om immuunbalans te herstellen

- Toekomst: gepersonaliseerde therapieën



Einde



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